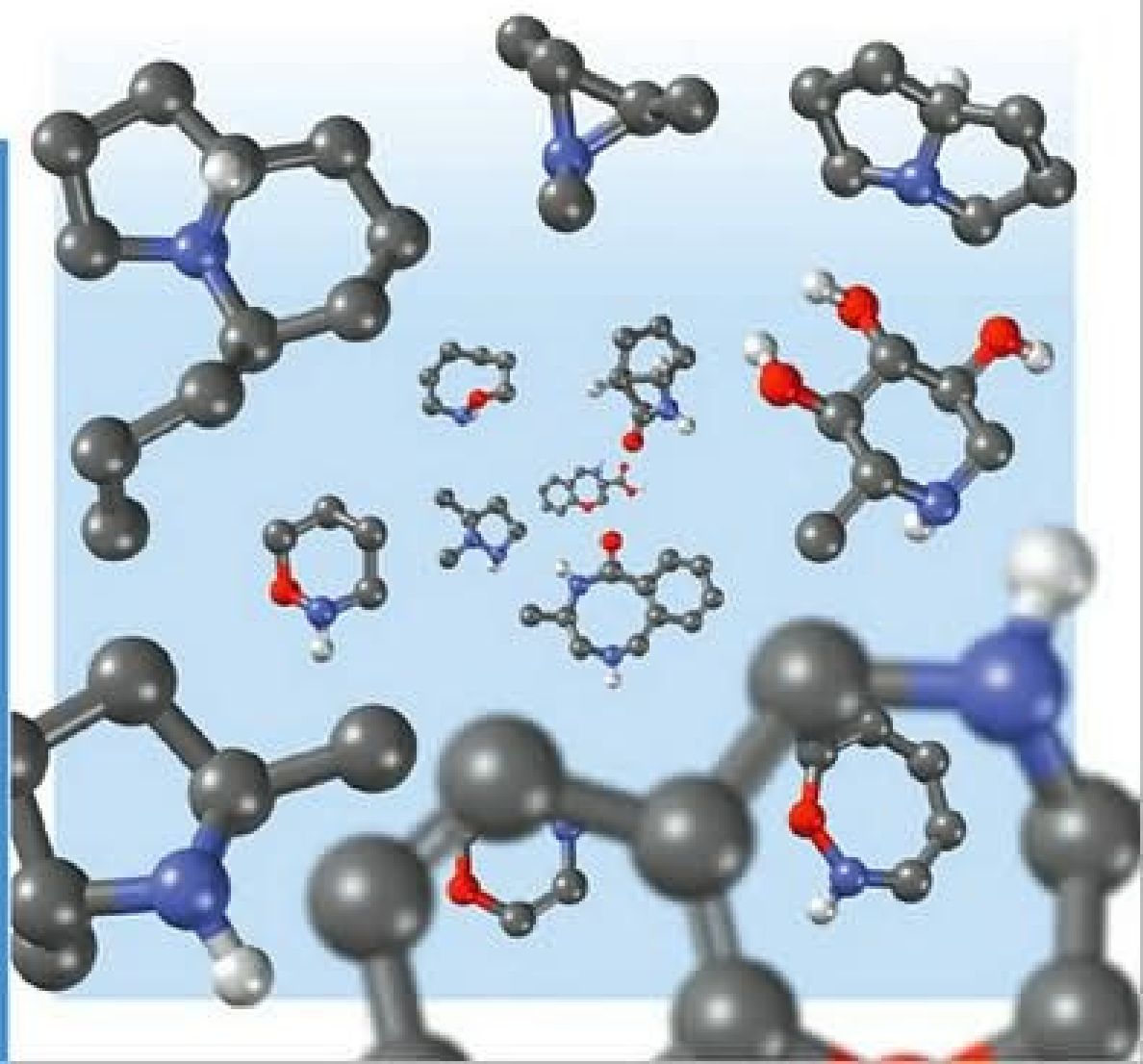


Edited by Jacques Royer

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# Asymmetric Synthesis of Nitrogen Heterocycles



**Asymmetric Synthesis of Nitrogen  
Heterocycles**

*Edited by*  
*Jacques Royer*

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# Asymmetric Synthesis of Nitrogen Heterocycles

*Edited by*  
*Jacques Royer*



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## Foreword

It is a great pleasure to see a new volume of *Asymmetric Synthesis of Nitrogen Heterocycles* going to press.

Since the nineteenth century, the study of nitrogen-containing products, especially alkaloids, has often provided the impetus for great advances in organic chemistry. On one hand, the unceasing proliferation of alkaloid literature accounts for the interest in this class of natural products. On the other hand, heterocyclic chemistry, in general, represents a special topic in medicinal chemistry. Moreover, optically active amines constitute an important class of compounds that find a wide range of interest as chiral building blocks and as part of many pharmaceutical products. Indeed, asymmetric synthesis is more than an academic specialty.

It is the goal of this book to bring all these aspects up to date and to extend the scope of asymmetric synthesis of nitrogen heterocycles to a large variety of structures, that is, with respect to ring size and number of heteroatoms. The objective of the Editor, who is also contributor of a chapter, has been reached in receiving the collaboration of leaders in this field from Europe, China and Japan.

This volume is divided into two parts. Part One describes in four chapters asymmetric synthesis of nitrogen heterocycles containing only one heteroatom in 3-, 4-, 5-, 6-, 7- (and more) membered rings. Part Two consists of four chapters covering the asymmetric synthesis of nitrogen heterocycles with more than one heteroatom.

I am sure that this treatise, which highlights an important field of enantioselective chemistry, should be of value to both academic and pharmaceutical chemists as well as PhD students.

Paris, October 2008

Professor *H.-P. Husson*



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## Preface

Nitrogen heterocycles are a huge family of compounds. Among them, numerous natural products as well as synthetic derivatives exhibiting some interesting biological activities can be found. Chirality is often encountered in such products since bioorganic substances such as receptors and enzymes are essentially asymmetric and thus their ligands are better to be asymmetric in order to fit with this asymmetric environment. On the other hand, natural nitrogen compounds are also mainly asymmetric.

Thus, the asymmetric synthesis of nitrogen heterocycles is a frequent preoccupation of organic chemists from both the academic and industrial areas. While the synthesis of nitrogen heterocycles uses several types of known classical reactions, it also has its own specificity shown through various strategies.

In this context, I had been keen on editing a book dealing with the “*asymmetric synthesis of nitrogen heterocycles*”. While several books dealing with nitrogen heterocycles already exist, no book or review article proposes an overview of the different methods used in their preparation in the asymmetric form according to their structure. It then appeared that there would be a need to have a review gathering such information.

I requested some colleagues to contribute the chapters in this book. They were all approached on the basis of their experience in and authoritative knowledge of specific nitrogen heterocycles.

In an attempt to cover most of the classical nitrogen heterocycles, the book has been divided into two parts. The first part deals with heterocycles bearing only one heteroatom in their ring; it is organized into chapters according to the size of the ring: aziridine, azetidine, pyrrolidine, piperidine, azepine and larger rings. The second part deals with heterocycles that contain at least two heteroatoms (one being nitrogen), here again, the chapters correspond to the size of the ring: from three to seven-membered rings. Each chapter is also carefully organized with the aim to provide easy access to information about the different heterocyclic structures. In summary, the main idea of this book is to furnish a comprehensive handbook giving firsthand information to researchers wanting to prepare chiral nitrogen heterocycles.

This book would be useful for organic chemists interested in the asymmetric synthesis of heterocyclic compounds including natural products and to those working in pharmaceutical companies or in academic institutions as well. It would also be helpful for graduate students.

I am deeply indebted to my colleagues who, knowing the time-consuming nature of this important piece of work, have contributed the articles for this book.

Paris, October, 2008

*Jacques Royer*

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## **Part One**

# **Asymmetric Synthesis of Nitrogen Heterocycles Containing Only One Heteroatom**



## 1

# Asymmetric Synthesis of Three- and Four-Membered Ring Heterocycles

*Giuliana Cardillo, Luca Gentilucci and Alessandra Tolomelli*

## 1.1

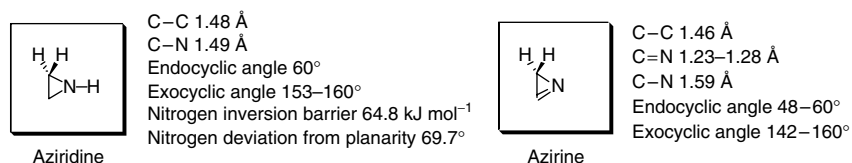
## Substituted Aziridines

## 1.1.1

### Generalities

Small heterocyclic rings constitute systems of central importance in theoretical, synthetic organic, bioorganic, and medicinal chemistry, and in particular aziridines and azirines are very useful and interesting systems as they occur in a number of natural and biologically active substances and as they are useful building blocks and versatile synthetic intermediates. Therefore, the development of efficient and stereoselective methods for synthesis and elaboration of aziridines is an inviting ongoing challenge [1]. Very often, stereogenic centers within such strained heterocycles can be used to direct the stereochemical outcome of subsequent transformations.

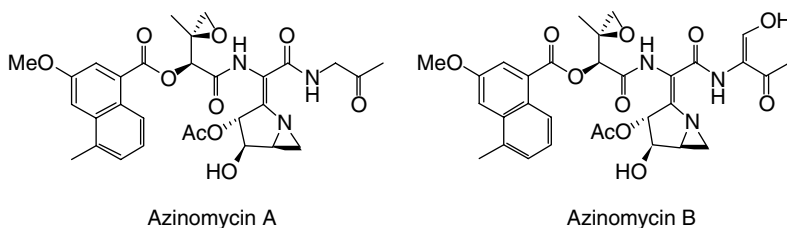
Aziridines and their dehydro derivatives, 2H-azirines, can be regarded as representatives of the first and most simple heterocyclic systems [2].



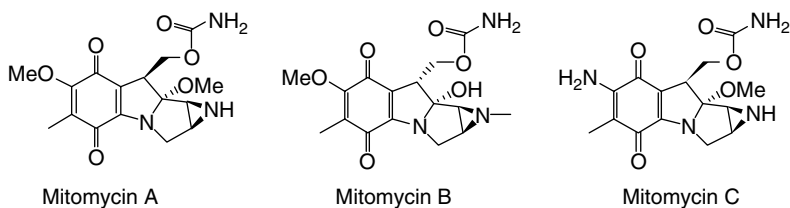
While numerous members of the aziridine ring systems are known and have been fully characterized, derivatives of the azirine ring system are mainly known as useful intermediates and only few examples of naturally occurring azirine derivatives have been reported.

Aziridines are present as structural motifs in a variety of strongly biologically active compounds such as azinomycins A and B [3], which are potent antitumors as well as antibiotic agents against both Gram-positive and Gram-negative bacteria

and have been isolated from the fermentation broth of *Streptomyces griseofuscus* S42227.



The antineoplastic activity of mitomycins A, B, and C [4], produced by *Streptomyces caespitosus*, is associated with the high reactivity of the strained heterocycle. Furthermore, some synthetic aziridines show strong activity as enzyme inhibitors [5], or are versatile intermediates for bioactive compounds.

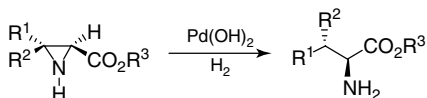


The first example of azirine-ring-containing natural compound was azirinomycin [6], an unstable antibacterial agent isolated from *Streptomyces aureus* fermentation broth in 1971. Only several years later, the cytotoxic compound dysidazine [7], the second structure showing the azirine motif, was extracted from *Dysidea fragilis*, a sponge collected in Fiji islands.

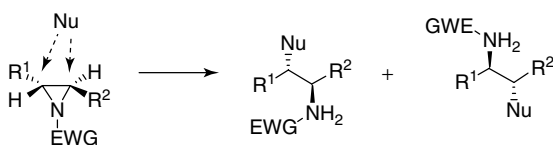
Since their discovery by Gabriel [8], aziridines have attracted attention as starting materials for further transformations in organic synthesis. The ring strain of aziridines, which amounts to 26–27 kcal mol<sup>-1</sup>, renders these compounds susceptible to ring opening with excellent stereo- and regiocontrol and allows their use as precursors of a variety of nitrogen-containing compounds such as amino acids, aminoalcohols, and  $\beta$ -lactams.

The main transformations of three-membered ring [9] are reported below:

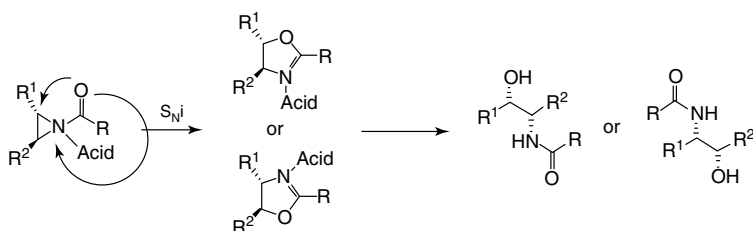
1. Hydrogenolysis: this allows chiral amine derivatives to be obtained via the regiospecific cleavage of a C–N bond. The process induces ring opening usually with inversion of the reacting stereocenter and without any modification of the stereochemistry at the unaffected carbon.



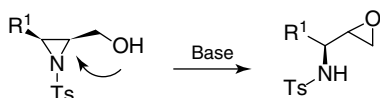
2. Hetero- and carbon nucleophile ring opening: this gives access to a variety of optically active ramified amines or amino alcohols, amino thiols, diamines, etc. While the reactivity of N-unsubstituted aziridines is relatively low, high reactivity is associated with aziridines incorporating an electron-withdrawing group on the nitrogen atom. For instance, the presence of an acyl group strongly activates the ring toward opening by a nucleophile. This reaction is generally favored by the presence of Lewis acids and proceeds with inversion of configuration at the stereogenic center of the aziridine. Unlike their acyclic amide counterparts, acylaziridines are highly pyramidalized at nitrogen, which makes the acyl-aziridine nitrogen more basic. The stereoselectivity is usually high and the regioselectivity depends upon the ring substituents and the nature of the nucleophile.



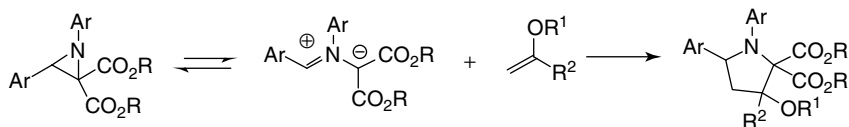
3. Ring expansion: this is another important reaction characteristic of N-acylaziridines, which represents the isomerization to the corresponding oxazolines, protected form of chiral amino alcohols. This reaction generally occurs in the presence of a Lewis acid and leads to the five-membered ring with retention of configuration.



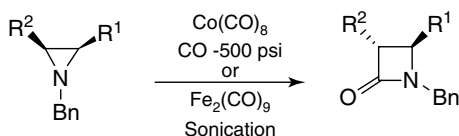
4. aza-Payne reaction: this is the rearrangement of aziridine-2-methanols under basic conditions to the corresponding epoxide-2-amines. These last compounds can be further transformed by reaction with nucleophiles.



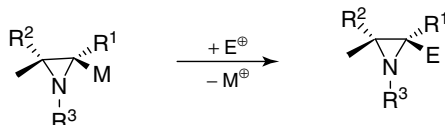
5. 1,3-dipolar cycloaddition of aziridine-2,2-dicarboxylates: this is an interesting reaction that involves generation of 1,3-dipoles from three-membered rings and  $\pi$  systems, giving access to larger size heterocycles.



6. Carbonylation: this allows the formation of  $\beta$ -lactams via insertion of the carbonyl group and inversion of configuration at the reacting carbon terminal.



7. Formation and reactivity of aziridinylium cations: these are stable species at low temperature, which may react with a variety of electrophiles allowing introduction of functionalized chains on the heterocycle.

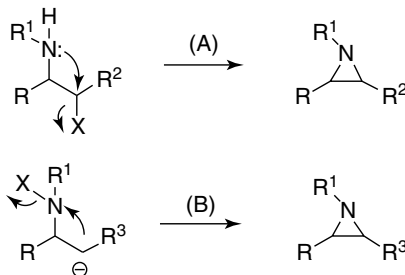


M = Li, Mg, Zn, Zr

### 1.1.2

#### Asymmetric Aziridination via Cyclization Methods

General approaches to the asymmetric synthesis of aziridines through cyclization methods can be divided into two main categories: (A) nitrogen nucleophilic cyclization on the adjacent position bearing a leaving group and (B) ring closure to three-membered ring via attack of a stabilized carbanion on the electrophilic nitrogen bearing a leaving group. The last approach is particularly suitable for the preparation of aziridine-2-carboxylates.



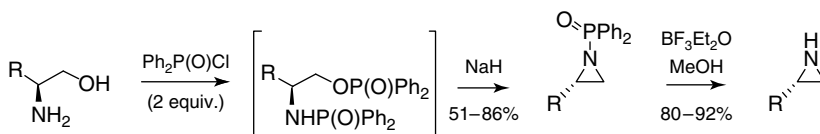
R<sup>3</sup> = Carboxylate

In both cases, the asymmetric induction may be exerted by the chirality of the substrate, by the introduction of a chiral auxiliary, by the presence of a chiral metal catalyst, or by the application of organocatalytic processes.

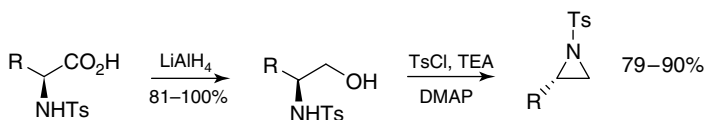
### 1.1.2.1 Cyclization of a Nucleophilic N on an Electrophilic C (Pathway A)

**Cyclization of Amino Alcohols** The most general and conceptually simple method for the synthesis of optically active aziridines is the cyclization of amino alcohols and amino halides. The availability of enantiopure amino alcohols directly from the chiral pool or by simple reduction of amino acids makes this approach extensively exploited. Protection of the amino function is sometimes required, and in these cases sulfonyl or phosphinyl groups are usually preferred to carbamates or acyl groups, to avoid competitive formation of larger heterocycles such as oxazolines or oxazolidinones.

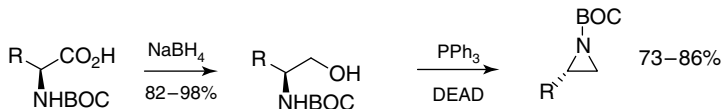
Thus, conversion of the hydroxyl moiety into a good leaving group such as tosyl [10], mesyl, nosyl, tetrahydropyranyl (THP) [11], diphenylphosphinyl (Dpp) [12], *t*-butyldimethylsilyloxy (TBS) [2] allowed the preparation of an activated intermediate to be easily converted to aziridine under basic conditions through an intramolecular  $S_N2$  reaction.



When reduction of the carboxylic function is needed to produce the proper aminoalcohol, *N*-tosyl amino acids have been used as reagents of choice to avoid difficulties in the isolation of water-soluble amino alcohols [10].



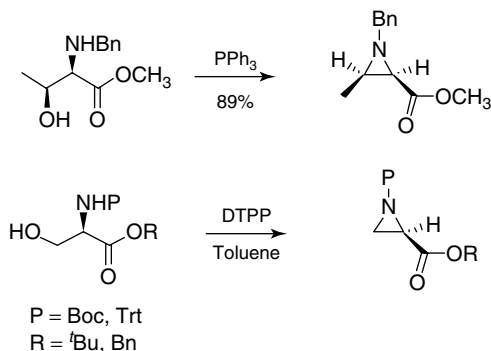
Activation of the hydroxyl function may be preformed also under Mitsunobu conditions. Treatment of *N*-Boc-amino alcohols, easily obtained by reduction of the corresponding amino acids, with triphenylphosphine and Diethyl azodicarboxylate (DEAD) afforded optically active *N*-Boc-aziridines in good yields [13].



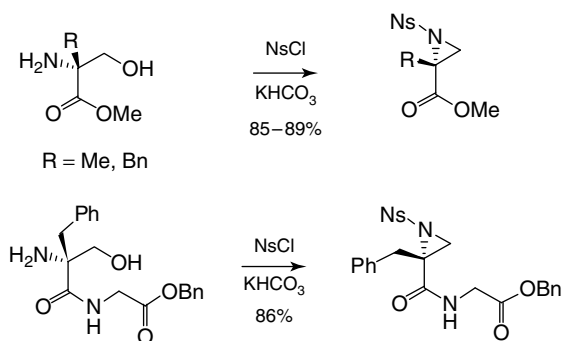
Aziridine-2-carboxylates have been successfully obtained starting from serine or threonine. Starting from *D*-threonine, Rapoport and coworkers [14] synthesized enantiopure *N*-benzyl-aziridine-2-esters by treatment with triphenylphosphine. On



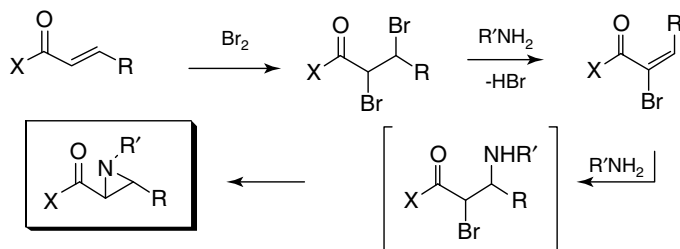
the other hand, ring closure of *N*-protected-serine esters with diethoxyphenylphosphorane (DTPP) gave aziridines-2-tert-butylate in satisfactory yield [15].



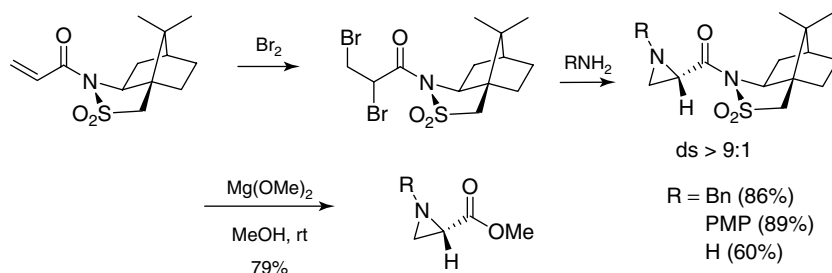
Generally, enantiopure aziridine-2-carboxylates are synthesized as precursors of  $\alpha$ - or  $\beta$ -amino acids in a multistep sequence directed to the preparation of bioactive peptides and peptidomimetics. To this purpose, Palomo and coworkers reported the easy formation of the aziridine ring by treatment of the dipeptide serine–glycine benzyl ester via nosylation of the oxygen atom under basic conditions. This procedure allowed the authors to reduce protection/deprotection steps, directly performing the reaction on glycine benzylester derivative [16].



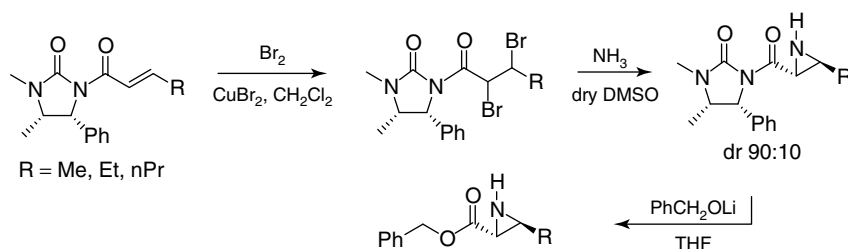
**Asymmetric Synthesis of Aziridines via Gabriel-Cromwell Reaction** The Gabriel-Cromwell reaction is a general and convenient method for aziridination of  $\alpha$ ,  $\beta$ -unsaturated compounds. Since its introduction in 1952 [17], many variations on the standard procedure have been explored to broaden the field of application. The reaction occurs via addition of bromine to the double bond followed by treatment with an amine. The mechanism proceeds with the formation of a dibromo derivative that converts to a  $\alpha$ -bromo-alkene through elimination of bromhydric acid. The conjugate addition of a second molecule of amine, followed by nucleophilic displacement of the bromine, leads to aziridine-carboxylate formation.



The asymmetric version of this reaction has been described using chiral auxiliaries such as camphor sultam [18]. Stereodefined 3-unsubstituted-aziridine-2-carboxylic acid may be prepared starting from acryloyl camphor sultam derivatives and by removal of the chiral auxiliary in a nondestructive manner in the final step. Repetition of aziridination protocol with *N*-crotonyl-camphor sultam resulted in the formation of 1:1 mixtures of easily separable aziridines.



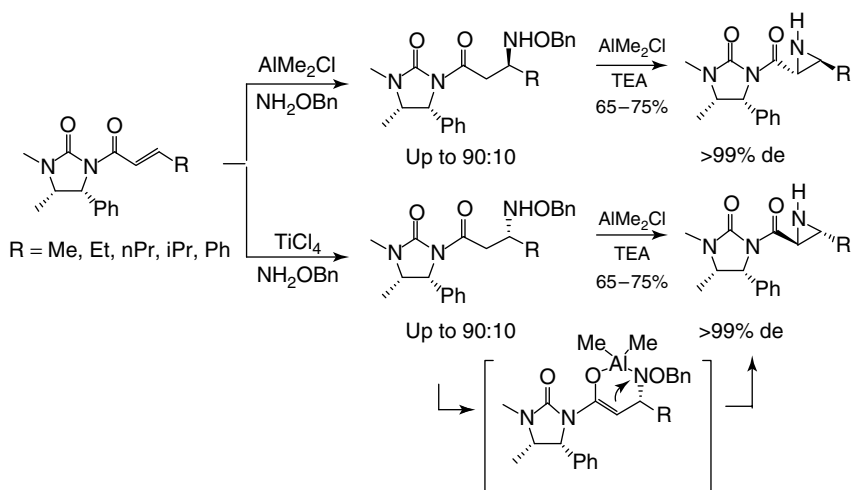
The asymmetric induction controlled by means of ephedrine-derived Helmchen's auxiliary gave better results [19]. Gabriel-Cromwell reaction on chiral imides in DMSO afforded via diastereoselective and high yielding procedure, optically active *trans*-aziridines, easily purified by flash chromatography. The nondestructive cleavage of the chiral auxiliary with lithium benzyloxide gave the corresponding enantiopure benzyl aziridine-2-carboxylates.



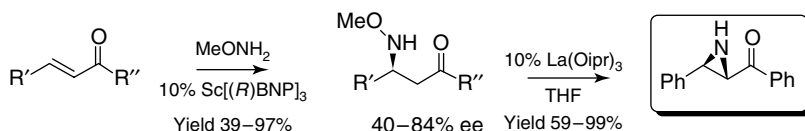
### 1.1.2.2 Cyclization of a Stabilized Anion on an Electrophilic N (Pathway B)

Starting from the unsaturated derivatives reported above, the same authors performed the diastereoselective synthesis of aziridine-2-imides via conjugate addition

of *O*-benzylhydroxylamine followed by cyclization to three-membered rings [20]. This second step was induced through the formation of the stabilized aluminum enolate of the addition product that spontaneously attacked the electrophilic nitrogen bearing the *O*-benzyl leaving group. Removal and recovery of the chiral auxiliary were performed as reported above.

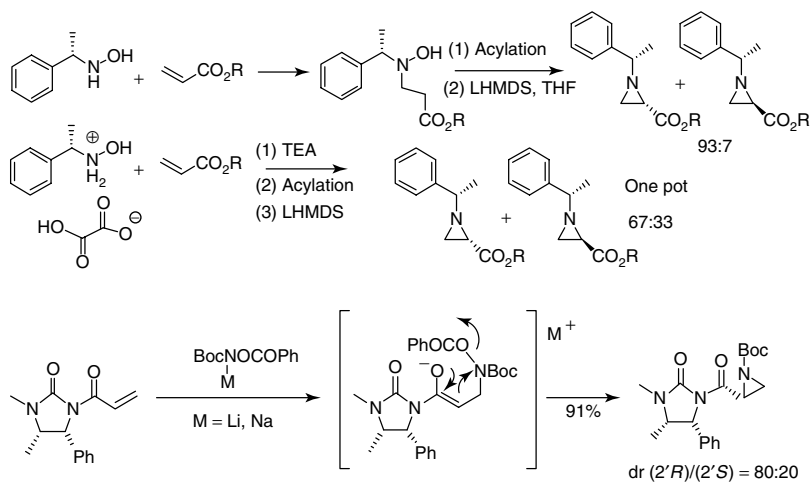


In a similar way, optically active 1*H*- $\alpha$ -keto aziridines were synthesized from conjugated enones via  $\text{Sc}[(R)\text{-BNP}]_3$ -catalyzed enantioselective Michael addition of *O*-methylhydroxylamine, followed by  $\text{La}(\text{O}i\text{Pr})_3$ -catalyzed ring closure [21].

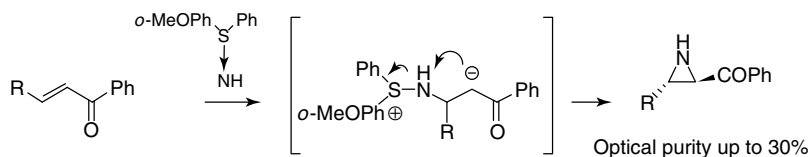


The products obtained by addition of chiral hydroxylamine to acrylates have been transformed into 2- and 2,3-disubstituted-*N*-alkylaziridinecarboxylate through an efficient diastereoselective 3-exo-tet ring closure induced by *O*-acylation of the diastereomeric adduct followed by enolization. This two-step protocol afforded optically active aziridines with excellent diastereoselectivity (93:7). Attempts to perform a one-pot two-step reaction resulted in a lower stereoselectivity (67:33) [22].

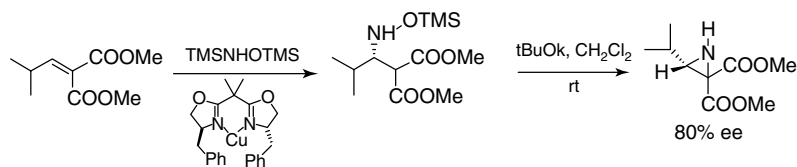
A further development of the same synthetic approach is represented by the synthesis of 3'-unsubstituted-*N*-Boc-aziridines, which has been carried out in one step by conjugate addition of sodium or lithium anion of *N*-Boc-*O*-benzoylhydroxylamine to chiral acryloyl-imides [23].



The Michael-type addition of (+)-(R)-o-methoxyphenylsulfonyl ethylsulfonamide to unsaturated carbonyl compounds afforded optically active *trans*-acylaziridines with modest stereoselectivity by displacement of the diphenylsulfide group from the intermediate enolates [24].

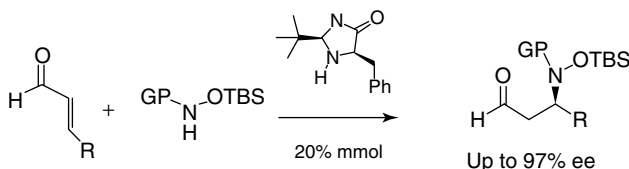


The addition of *N*, *O*-bis(trimethylsilyl)hydroxylamine to alkylidene malonates in the presence of a catalytic amount of  $\text{Cu}(\text{OTf})_2$  and chiral bisoxazoline as ligand, followed by base-induced cyclization, represents a useful route to enantiomerically enriched aziridine-2,2-dicarboxylates. This two-step protocol afforded the three-membered rings with good yield and enantiomeric excesses up to 80%, depending on the substituent on the alkylidene double bond [25].

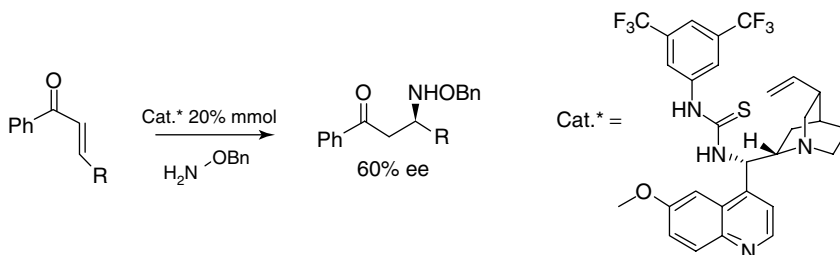


In general, the conjugate addition of hydroxylamines to unsaturated carbonyl derivatives is one of the most convenient methods for the stereoselective synthesis of  $\beta$ -hydroxylamino-carbonyl building blocks, which are useful intermediates in the preparation of enantiopure aziridines. Asymmetric methods dealing with stoichiometric use of chiral auxiliaries in the presence of Lewis acids or with the use of catalytic amount of chiral metal complexes have been exhaustively reviewed [26].

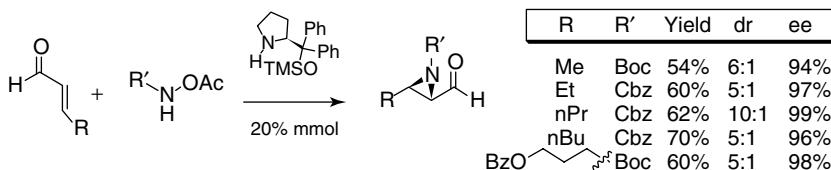
The organocatalytic version of the aza-Michael addition was less explored. MacMillan and coworkers reported the first organocatalytic addition of *N*-silyloxy-carbamates to unsaturated aldehydes, giving access to aziridine precursors [27].



In a recent report, the conjugate addition of *O*-benzylhydroxylamine to chalcones was performed in the presence of thiourea-derived catalysts. Although a screening of solvents, *O*-substituted hydroxylamines, and chiral ligands was performed, moderate enantiomeric excesses up to 60% could be observed [28].



The organocatalysis may be applied to aziridination when the substrate to be transformed is an aldehyde. In fact, the highly chemo- and enantioselective organocatalytic aziridination of a variety of  $\alpha$ ,  $\beta$ -unsaturated aldehydes with acetyloxy carbamates was developed. The reaction was catalyzed by chiral pyrrolidine derivatives and gave Boc- or Cbz-2-formylaziridines in yields ranging from 60 to 70%, with dr 4:1–19:1 and 84–99% ee [29].



### 1.1.3

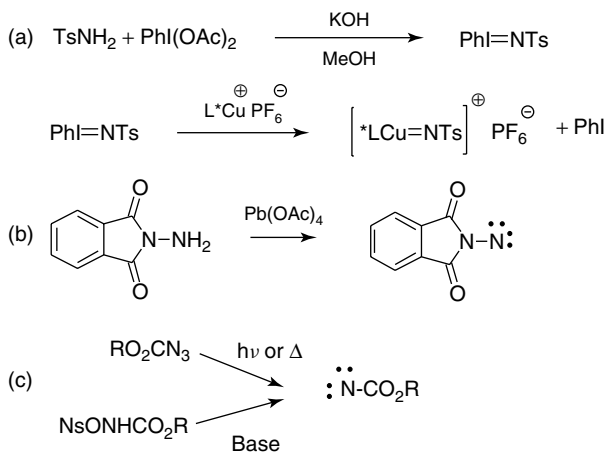
#### Asymmetric Aziridination via Cycloaddition Methods

##### 1.1.3.1 Addition of Nitrenes to Alkenes

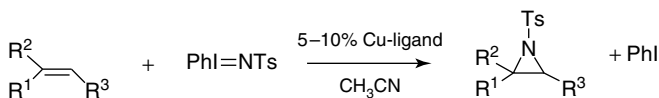
One of the most important pathways to aziridines is the addition of a nitrene to an alkene; however, this reaction may not be well controlled stereochemically owing to the rapid interconversion of the singlet and triplet nitrene states. Anyway,

several methods for nitrene generation have been successfully developed with the aim to obtain stereospecific aziridination. The most common involve photolysis, thermolysis, or chemical modification of nitrogen derivatives.

Many chiral metal catalysts have been used to induce nitrene formation from N-substituted iminoiodinanes, although this method produces stoichiometric amount of iodobenzene and yields N-protected aziridines. The use of azide precursors gives some advantage in terms of atom efficiency and environmental impact since molecular nitrogen is the only side product. Nosyloxycarbamates and N-aminophthalimides are also alternative sources of nitrene.

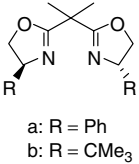
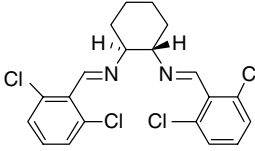
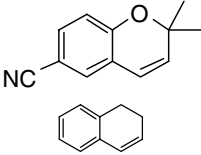

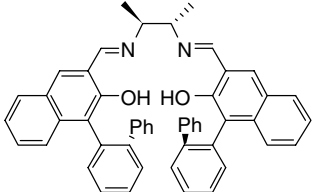


N-(*p*-toluenesulfonyl)iminophenylidiodane ( $\text{PhI} = \text{NTs}$ ) [30] (source a) proved to be superior to other imido group donor as precursor and yielded excellent stereoselectivity. In 1991, Evans and coworkers disclosed that low-valent copper complexes catalyze the aziridination of several different olefins by this reagent. Development of the enantioselective process consists in the use of chiral bisoxazoline catalysts. Some selected results are reported in Table 1.1.



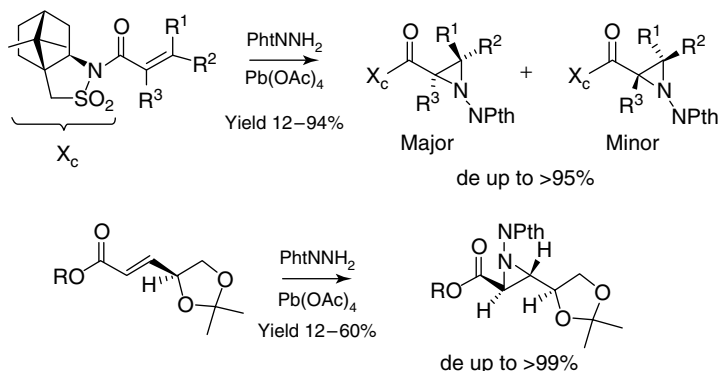
Aryl-substituted olefins have been found as good substrates, which can be efficiently transformed into N-tosyl-aziridines with enantioselectivities up to 97% ee (entries 1–4) [31]. The reactions have been carried out with 5% of chiral catalyst derived from copper(I) triflate and bisoxazoline as ligand. Unfortunately, tartrate-derived bisoxazoline gave only low enantiomeric excess (2–49% ee). A complete study on the effect of bisoxazoline substituents and reaction conditions on this reaction has been reported by Page and coworkers [32]. Some improvements of both enantioselectivity and chemical yields were obtained when [N-(4-nitrobenzenesulfonyl)imino]phenylidiodane was employed instead of the

**Table 1.1** Enantioselective aziridination with *N*-aryl-iminophenylodine and chiral metal complexes

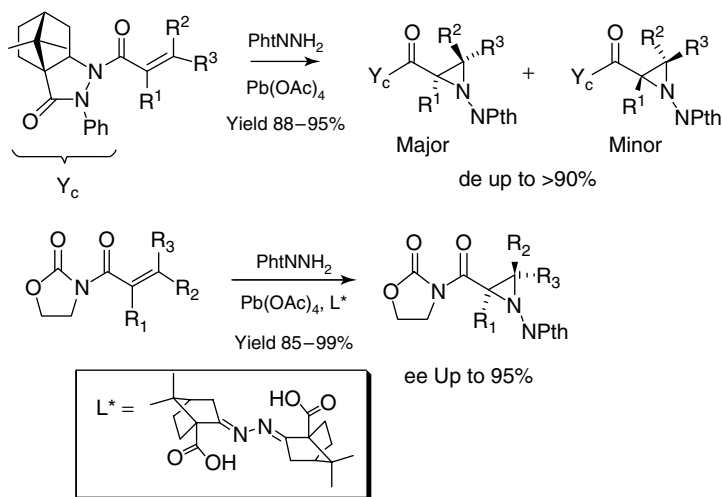
Entry	Chiral ligand	Olefin	Catalyst	Nitrene precursor	Yield	ee
1	 a: R = Ph b: R = CMe <sub>3</sub>	Ph-CH=CH-CO <sub>2</sub> Ph	a	PhI = NTs	64	97
2		( $\alpha$ )Nap-CH=CH-CO <sub>2</sub> Me	a	PhI = NTs	76	95
3		Ph-CH=CH-Me	b	PhI = NTs	62	70
4		Ph-CH=CH-H	b	PhI = NTs	89	63
5		Ph-CH=CH-Me	b	<i>p</i> -NO <sub>2</sub> -PhI = Ts	83	80
6		Ph-CH=CH-H	b	<i>p</i> -NO <sub>2</sub> -PhI = Ts	94	66
7		Ph-CH=CH-H		PhI = NTs	79	66
8				PhI = NTs	75	>98
9				PhI = NTs	70	87
10		Ph-CH=CH-H	Mn	PhI = NTs	76	94

commonly used *p*-tolyl analog (entries 5–6) [33]. In a similar way, Jacobsen and coworkers [34] obtained excellent results in the aziridination of benzylidene derivatives with chiral copper complexes deriving from bis(benzylidene)imine of 1,2-diaminocyclohexane (entries 7–9). The asymmetric aziridination of styrene derivatives has also been successfully performed with Salen-Mn(III) complexes (entry 10) [35].

Phtalimidonitrene (source b), generated from *N*-aminophthalimide by oxidation with lead tetraacetate, reacted with *N*-enoylbornane[10,2]sultams (Oppolzer auxiliary) to give the corresponding *N*-phtalimidoaziridine adducts in 12–94% yield and diastereofacial selectivity up to >95% [36]. In a similar way, excellent diastereoselection could be obtained by the addition of phtalimidonitrene to sugar-derived  $\alpha$ ,  $\beta$ -unsaturated esters [37].

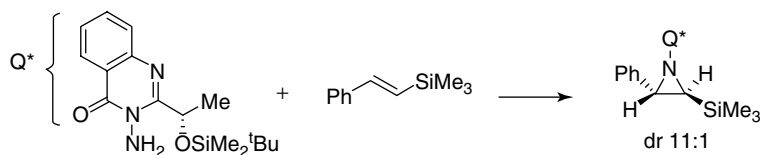


Chen and coworkers applied this methodology to the diastereoselective aziridination of  $\alpha,\beta$ -unsaturated amides linked to a camphor pyrazolidinone-derived chiral auxiliary [38]. The reactions carried out in 5 min afforded excellent yield (86–95%) of diastereomeric aziridines with high selectivity (up to >90% de). In pursuing this work, the same author reported the enantioselective version of this protocol, by performing the lead tetraacetate oxidative addition on *N*-enoyl oxazolidinones in the presence of camphor-derived chiral ligands [39].

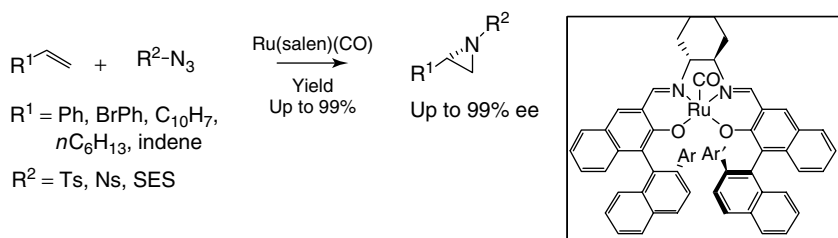


Besides the use of a chiral auxiliary linked to the alkene reagent or of chiral complexes of lead tetraacetate, another possibility is the use of chiral aziridinating agents. Atkinson and coworkers [40] reported that enantiopure 3-acetoxaminoguinazolinones react with  $\beta$ -trimethylsilylstyrene affording 11:1 ratio of diastereomeric aziridines.

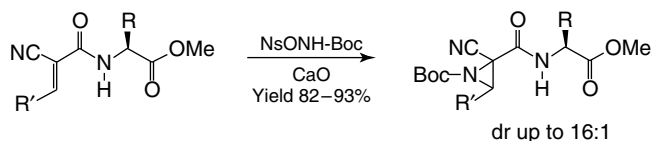




Organic azides (source b) may be considered as ideal sources of nitrenes although they are not very reactive and harsh conditions, such as heating or UV irradiation, are generally needed for molecular nitrogen dissociation. Initial attempts to perform asymmetric aziridination using azides and chiral metal catalysts have been reported by Jacobsen with Cu-diimine complexes and by Müller and co-workers using chiral Rh-complexes. In both cases, the nitrene generation was induced by UV irradiation. On the other hand, excellent yields (up to 99%) and enantioselectivities (up to >99% ee) have been obtained by Katsuki and coworkers in the presence of ruthenium(CO)(salen) complexes and tosyl azide. Under these conditions, neither heating nor irradiation was required for nitrene formation. The method is of general application since it has been successfully applied to a number of different olefins, changing the substituent of the chiral ligand and generating the nitrene reagent starting from different organic azides.



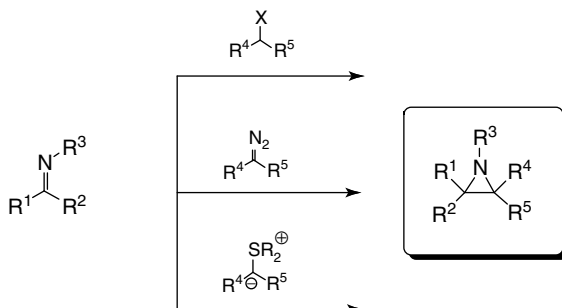
Finally, nitrenes may be formed from *N*-protected nosyloxycarbamate by treatment with a base such as CaO. Pallacani and Tardella applied this method to the synthesis of a variety of substituted *N*-protected aziridines [41]. Recently, excellent diastereoselectivity was observed in the aziridination of 2-*L*- $\alpha$ -aminoacyl-(*E*)-acrylonitriles under parallel solution-phase conditions [42].



### 1.1.3.2 Reaction between Carbenes and Imines

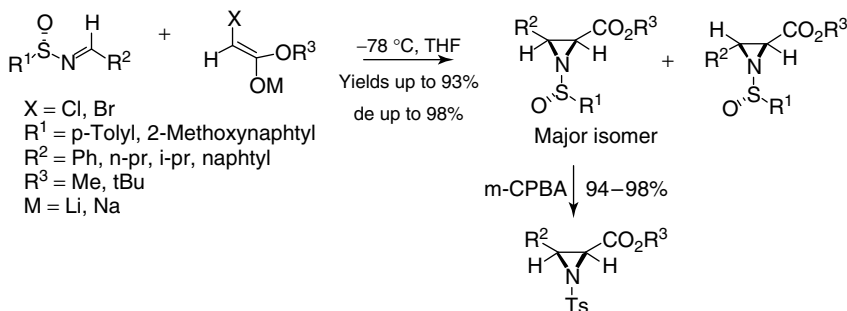
Among several synthetic routes, the classic methods involving imines have been upgraded to their asymmetric version inducing enantiocontrol by the use of chiral imines, chiral nucleophiles, or chiral catalysts. All these approaches share as

common feature the addition of a nucleophile on the electrophilic imine carbon, followed by cyclization to the three-membered heterocycle.



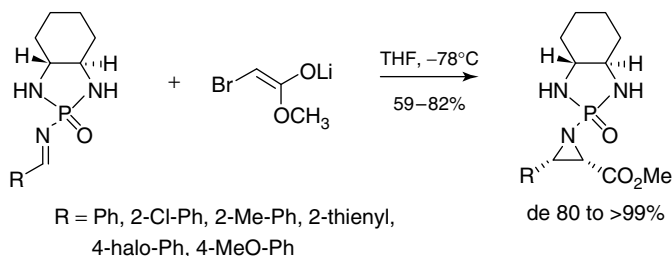
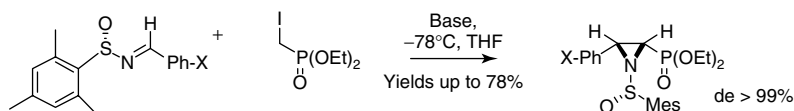
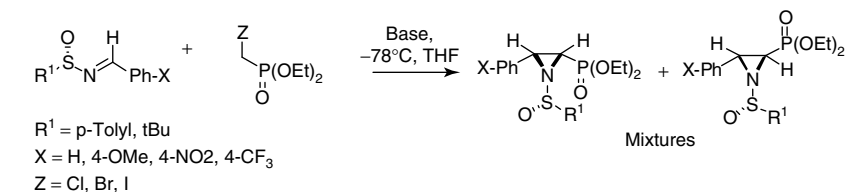
**aza-Darzens-Type Reactions Involving  $\alpha$ -Haloenolates** The aza-Darzens reaction between a  $\alpha$ -haloenolate and an imine can be considered a not fully investigated tool for the asymmetric synthesis of aziridines.

Davis and coworkers obtained excellent results in the synthesis of *N*-sulfinylaziridine-2-carboxylates by reacting enantiopure chiral sulfinimines with  $\alpha$ -bromo-enolates. The method is general for aliphatic, aromatic as well as  $\alpha$ ,  $\beta$ -unsaturated imines, giving good yields and de up to 98%, *N*-sulfinyl-heterocycles, which are easily transformable into activated *N*-tosyl-aziridines [43].

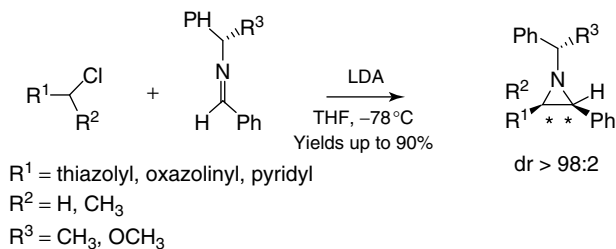


Following the same procedure, enantiopure aziridine-2-phosphonates were obtained from sulfinimines and halomethylphosphonates. A further improvement could be obtained employing *N*(2,4,6-trimethylphenylsulfinyl)imines and lithium diethyldiiodophosphonate [44].

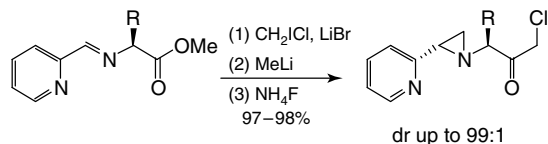
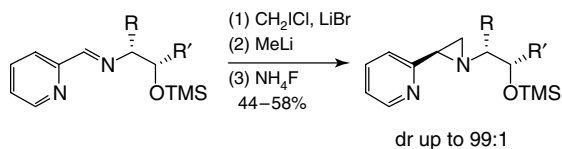
Despite the excellent results obtained with chiral sulfinimines, development of new chiral imines could overcome shortcomings as sensitivity to oxidative conditions and destructive chiral auxiliary removal. The reaction between chiral *N*-phosphonimines and  $\alpha$ -bromo-enolates gave *N*-phosphonylaziridines with excellent yield and high stereocontrol. The electrophilicity of the imine can be controlled by introducing electron-donating or electron-withdrawing groups onto phosphonate chiral auxiliary [45].



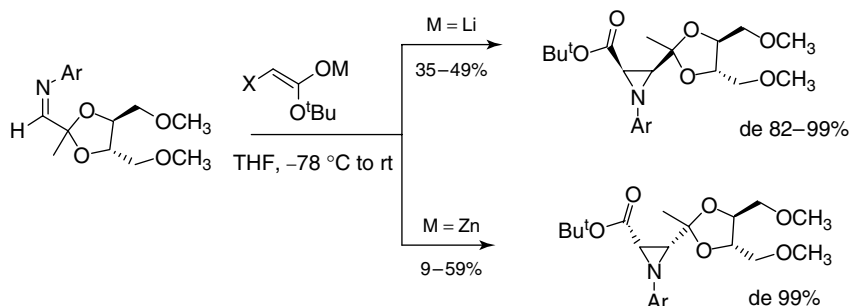
Chiral heterosubstituted aziridines have been obtained by the coupling of lithium enolates derived from ( $\alpha$ -chloroalkyl)heterocycles with various enantiopure imines, which are obtained from nonracemic phenylethylamine. The reaction afforded chiral aziridines with complete stereocontrol. The steric hindrance and the coordination power of the alkyl group linked to the iminic nitrogen are responsible for the stereochemistry of the final product [46].



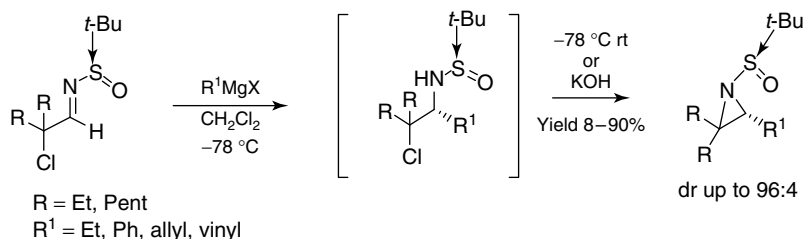
In a similar way, the addition of chloromethyl lithium to the imine derived from 2-pyridinecarboxaldehyde and chiral aminoalcohol or aminoesters gave disubstituted aziridines with good yields and excellent diastereoselectivity. In the latter case, double addition of the organometallic reagent occurred, affording aziridines having a keto function in the side chain [47].



Enantiopure *N*-acylaziridines have been obtained starting from aldimine bearing the chiral auxiliary into the carbon side chain. Under these conditions, complete inversion of diastereocontrol was induced by changing the metal counterion of the bromoenolate from lithium to zinc [48].

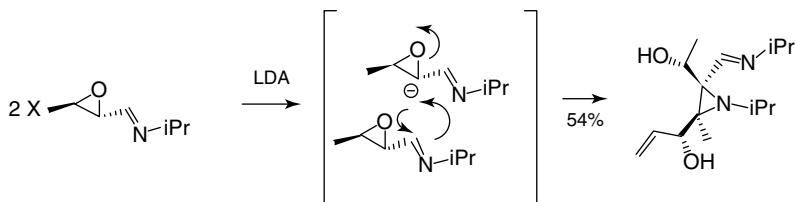


Similarly to aza-Darzens mechanism, the addition of organometallics as Grignards to chiral sulfinylimines bearing a  $\alpha$ -halogen leaving group followed by treatment with a base represents a high yielding route to optically active *N*-sulfinylaziridines. In this reaction, spontaneous or base-induced cyclization of the non-isolated intermediate  $\beta$ -halo-*N*-sulfinamides affords the three-membered rings in high yield and excellent diastereomeric ratio [49].



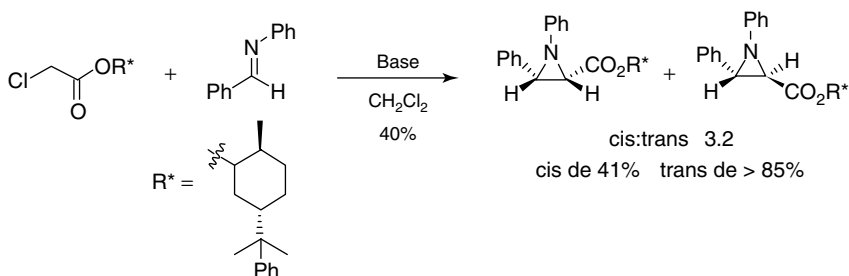
An application of aza-Darzens-type reaction has been performed to obtain polyfunctionalized aziridines through the base-induced dimerization of oxiranylaldehydes. This highly diastereoselective process is noteworthy since both nucleophile and electrophile originate from the same precursor. The nucleophilic moiety

is the 1-aza-allylanion having the epoxide at the  $\beta$  carbon and the leaving group is represented by the oxirane oxygen atom [50].

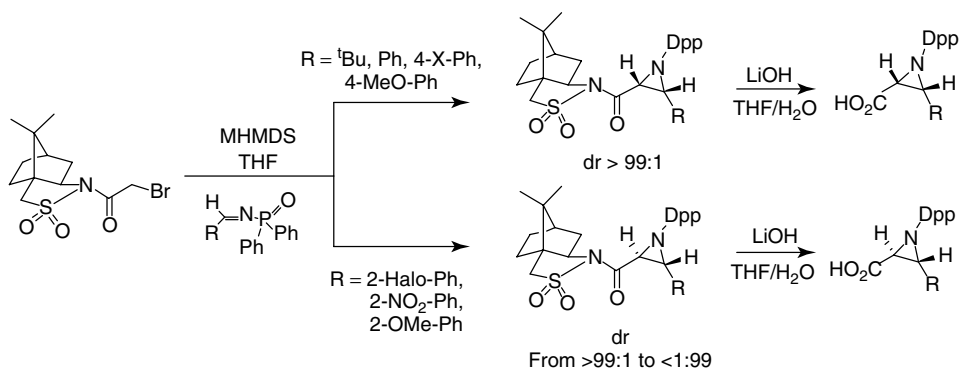


Asymmetric induction in the condensation between imine and haloacetates may be also obtained introducing chiral auxiliaries into the  $\alpha$ -haloacetate counterpart.

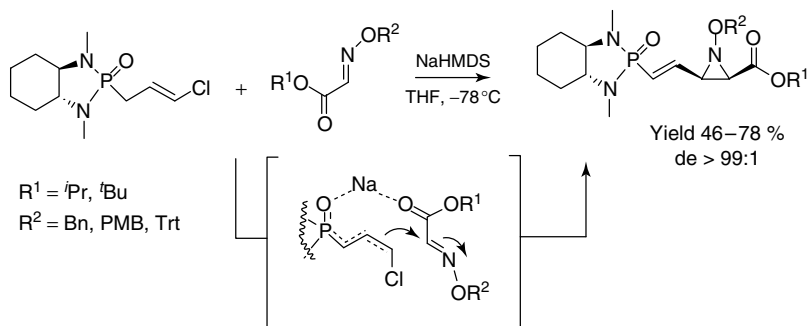
For instance, (+)-8-phenylmenthyl esters gave aziridine-2-carboxylates only in 40% yield and as diastereomeric mixtures of cis/trans heterocycles. Anyway, the diastereomeric excess of the trans isomer reached 85% [51].



On the other hand, camphorsultam-derived  $\alpha$ -bromo enolates reacted with N-Dpp-imine to afford a single cis diastereoisomer in high yield. Removal of the chiral auxiliary was simply performed with LiOH at room temperature. The method was successfully applied to aromatic, para-substituted aromatic, unsaturated, and aliphatic enolates. The introduction of an ortho substituent into the aromatic ring determined the stereoselectivity inversion, often giving exclusively trans products [52].

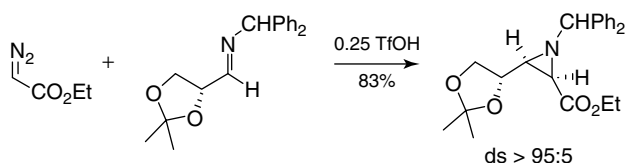


Finally, enantiopure *cis* *N*-alkoxy-aziridine-carboxylates have been obtained via aza-Darzens like reaction between the anion of optically pure chloroallyl phosphonamide and oximes. The reaction occurred in good to excellent yields through the approach of the oxime on the less hindered left cleft of the phosphonamide anion, giving a single diastereoisomer [53].



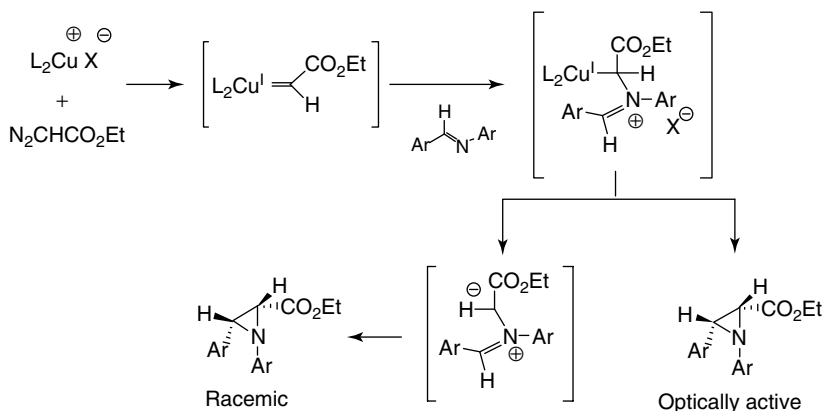
**aza-Darzens-Type Reactions Involving Diazo Compounds** This methodology, involving the formation of a metal–carbene intermediate complex that adds to an imine, shows several advantages of other synthetic approaches since the reagents are synthetically accessible and highly reactive and the only by-product is represented by molecular nitrogen. The asymmetric version of this reaction has been successfully developed using enantiopure starting materials, stoichiometric amounts of chiral auxiliaries linked to the reagent backbone, or by catalyzing the reaction with chiral Lewis acids.

The protocol recently reported by Johnston and coworkers, based on the Brønsted acid-catalyzed annulation, afforded enantiopure aziridine-2-carboxylates by using glyceraldehyde as chiral auxiliary. The diazocompound reacted as enolate synthon without any decomposition, giving the product in 83% yield and complete diastereoselectivity [54].

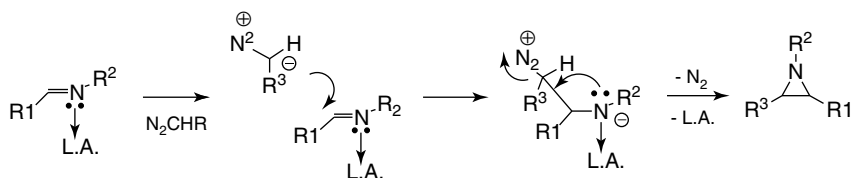


The asymmetric metal-catalyzed transfer of diazocarbonyl-derived carbene to imines represents the most explored approach. To this purpose, Jacobsen and coworkers investigated copper(II) complexes catalyzed aziridination of *N*-benzylidene aniline and diazoacetate [55]. Although *cis*-aziridines were obtained only in modest yields (5–65%) and stereoselectivities (2–67% ee), a deep exploration of the reaction mechanism allowed to suggest the generation of a transient bis(dihydrooxazole)copper carbene complex that reacts with the imine to form a

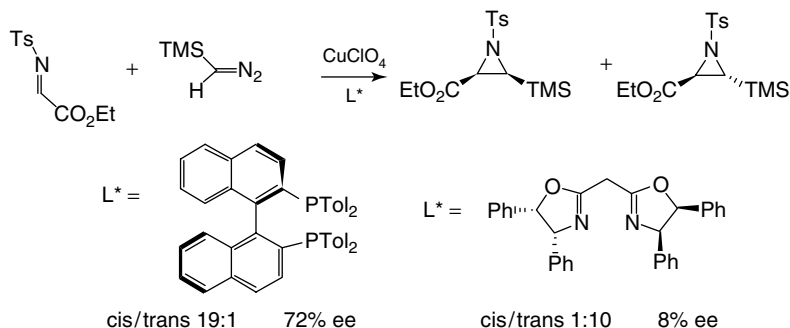
metal-complexed azomethine ylide. This intermediate may undergo intramolecular ring closure to optically active aziridine or it may dissociate to free azomethine ylide, precursor of the formation of racemic aziridine. This investigation outlined the influence of the chiral ligand on the metal-complexed azomethine ylide evolution, thus providing useful information for enantioselectivity enhancement.



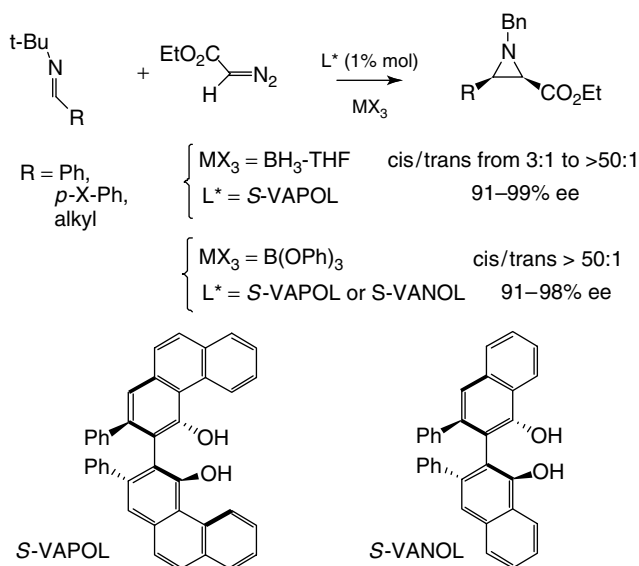
On the other hand, Jørgensen and coworkers explored the reaction of imines with diazoacetate. In the course of this study, they proposed a second possible mechanism involving the coordination of the Lewis acid to the nitrogen atom of the imine, followed by the nucleophilic attack of diazoacetate on the C=N double bond and by the ring closure on the carbon bearing N<sub>2</sub> leaving group [56].



Extension of this approach to the reaction of  $\alpha$ -imino esters in the presence of chiral ligands allowed the development of a catalytic diastereo- and enantioselective aziridination of imines derived from  $\alpha$ -ethylglyoxylate. Bisoxazolines, phosphinoxazolines, and bis(phosphino)-binaphthyl ligands were tested in combination with AgSbF<sub>6</sub> or CuClO<sub>4</sub>. High diastereoselectivity in *cis*-aziridine formation was observed using (*R*)-Tol-BINAP (*cis/trans* 19:1) with a good enantiomeric excess (72%), while the *trans* isomer was obtained as major product in the presence of (4*R*, 5*S*)-Ph-BOX [57].

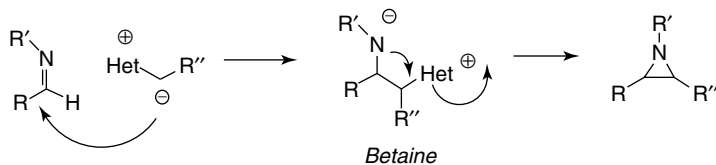


One of the best generally applicable method for the catalytic asymmetric aziridination was presented by Wulff and Antilla, using a catalyst prepared from VAPOL and borane-tetrahydrofuran. Under these conditions, excellent yields and high asymmetric induction were obtained in the reaction of benzhydrylimines with ethyl diazoacetate using 1% mol of the chiral catalyst [58]. A further enhancement of cis/trans selectivities (up to >50:1), yields (up to 91%), and enantiomeric excesses (90–98%) could be obtained using VAPOL or VANOL ligands in the presence of triphenylborate [59].



**Aziridination by Reaction of Imines with Ylides** Besides  $\alpha$ -halo derivatives and diazo compounds, also ylides were reacted with imines in the asymmetric ring-closure to aziridine. The initial attack of the ylide to the electrophilic imine carbon affords a betaine, which evolves to aziridine via intramolecular ring closure and elimination of ylide heteroatom.

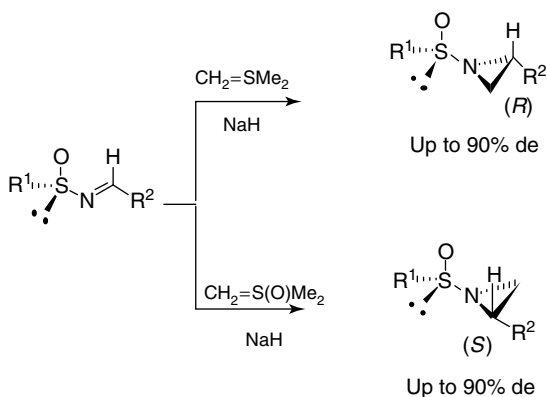




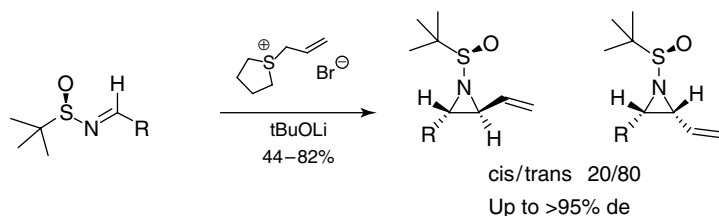
This methodology has been mainly applied to the preparation of enantiopure terminal-, alkyl-, aryl-, propargyl-, and vinyl-substituted heterocycles, by using methylene sulfur ylides as reagents.

The asymmetric induction in this reaction has been obtained introducing a stereocenter on the nitrogen imine side chain or generating sulfur ylides from chiral sulfides.

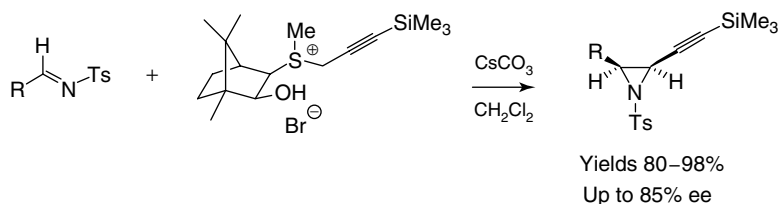
Following the first approach, Garcia Ruano and coworkers performed the reaction between enantiopure *N*-tolylsulfinylimines and dimethyloxosulfonium methylides and dimethylsulfonium methylides [60]. Optically active imines were easily generated by applying the “DAG methodology”, where diacetone-*d*-glucose was used as an inducer of chirality [61]. Under these conditions, the formation of terminal aziridines occurred with good to excellent diastereoselectivities (up to 95:5) and the enhancement of the stereocontrol was obtained by increasing the bulkiness of substituents. The opposite diastereoselectivity observed in the aziridination of dimethyloxosulfonium methylides and dimethylsulfonium methylides was explained by the authors, who suggested a thermodynamic control for the reaction of the first reagent and a kinetic control for the second one.



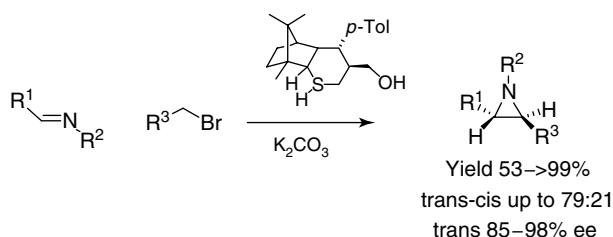
In a similar way, vinyl aziridines were obtained by Stockman and coworkers by treatment of chiral *tert*-butylsulfinylimines with the ylide generated by deprotonation of *S*-allyl tetrahydrothiophenium bromide. Using these methodologies, good yields (44–82%) and satisfactory *cis/trans* selectivities, always around 20/80, could be observed. On the other hand, aziridines were always obtained in excellent diastereoselectivity (up to >95%), thus demonstrating the efficiency of *tert*-butylsulfinyl group as activating and directing group [62].



Dai and coworkers [63] were able to perform the enantioselective synthesis of acetylenylaziridines owing to the introduction of chirality on ylides. Propargylic sulfonium ylides, generated in situ under phase transfer conditions, reacted with *N*-sulfonylimines to give acetylenylaziridines in excellent yields (80–98%). In most cases complete diastereoselectivity could be achieved to give exclusively *cis* heterocycles, although with enantiomeric excesses not higher than 85%.

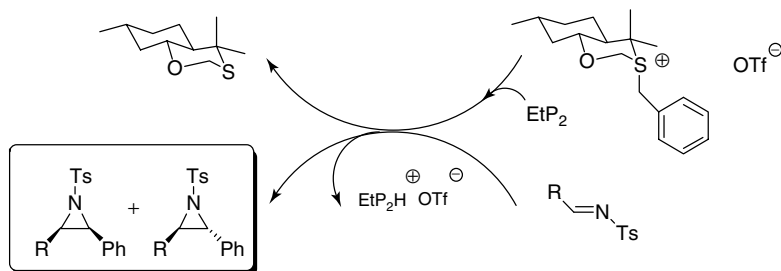


In a similar way, Corey-Chaykovsky reaction between *N*-sulfonylimine, arylmethylbromide, chiral sulfide, and a base by solid–liquid phase transfer conditions allowed Saito and coworkers [64] to synthesize enantiopure aziridines. The reaction occurs via the formation of a sulfonium ylide from the coupling of the sulfide with the halide, followed by deprotonation with the inorganic base. Excellent yields were obtained with imines bearing electron-withdrawing substituents on nitrogen atom.



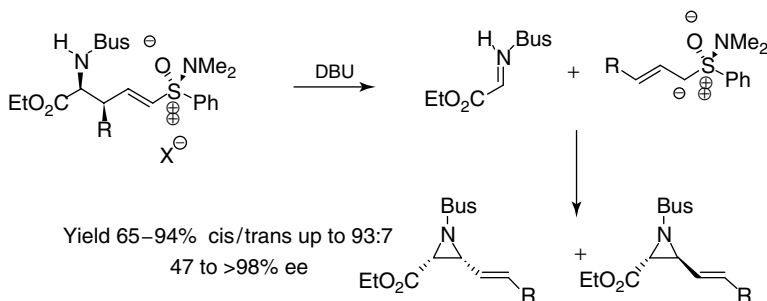
On the basis of the excellent results reported for oxathianes as precursors of enantiopure ylides in asymmetric synthesis, Solladiè-Cavallo and coworkers [65] developed a two-step asymmetric process for the preparation of enantiopure disubstituted *N*-tosyl-aziridines using a phosphazene base to generate the ylide. Although stoichiometric amounts of oxathiane are required in this reaction, complete recovery and recycle of this reagent are possible. Furthermore, no unstable or hazardous reagents are involved. Under these conditions, complete conversion of the starting

material into *cis/trans* mixtures of aziridines was observed. Both diastereoisomers have exceptionally high enantiomeric purities (98.7–99.9%).



Yield 60–88 % *cis/trans* up to 100/0  
98.7–99.9% ee

Generation of the two reagents for aziridination was also carried out by treatment of an aminosulfoxonium-substituted  $\beta$ ,  $\gamma$ -unsaturated  $\alpha$ -amino acid with a base. Fragmentation of the anion indeed affords a conjugated allyl aminosulfonyl ylide and an *N*-*tert*-butylsulfonyl-imino ester. Recombination of these two molecules gave *cis*-vinyl aziridine in almost quantitative yield and excellent diastereoselectivity and enantioselectivity [66].

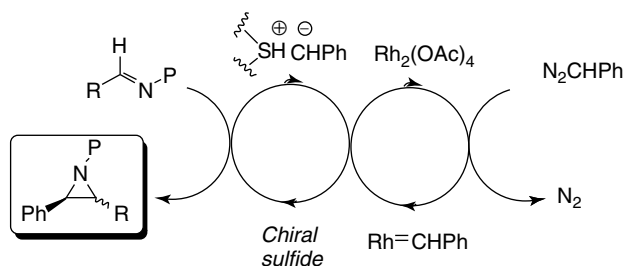


Yield 65–94% *cis/trans* up to 93:7  
47 to >98% ee

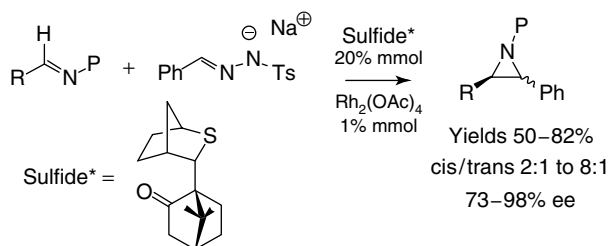
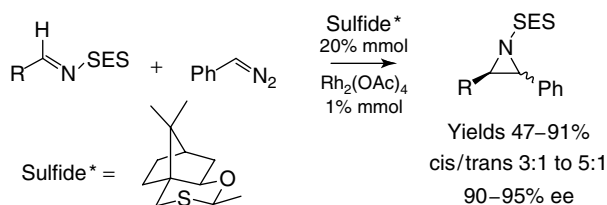
The asymmetric aziridination involving addition of sulfur ylides to imines normally requires stoichiometric amounts of enantiopure reagents. The first catalytic asymmetric application of this reaction was reported by Aggarwal and coworkers, wherein imines bearing an electron-withdrawing group on the nitrogen atom reacted with diazocompounds in the presence of chiral sulfide (20 mol%) and rhodium or copper salts (1 mol) [67].

The reaction proceeds following the catalytic cycle as reported in the figure below, affording optically active aziridines in excellent yields.

A complete study on the relevant factors governing stereocontrol allowed to establish that the origin of diastereoselectivity lies for semistabilized ylides (benzylic) in the nature of transition states leading to betaines, while for stabilized ylides (ester/amide) in the nature of the transition states leading to ring closure [68]. On the other hand, the enantioselectivity is always very high and may be attributed to



both steric and electronic factors in ylide preferred conformation (trimethylsilylthanesulfonyl (SES)). It is noteworthy that the parallel reaction of diazocompounds with imines is very limited and does not significantly affect yield and stereocontrol. Although higher yields could be obtained using stoichiometric amount of chiral sulfide, reduction to catalytic amount did not result in lower stereoselectivity. To overcome potential problems due to hazardousness of large-scale reactions, the diazo compound was generated in situ and a new class of sulfides, compatible with reaction conditions, was developed [69].



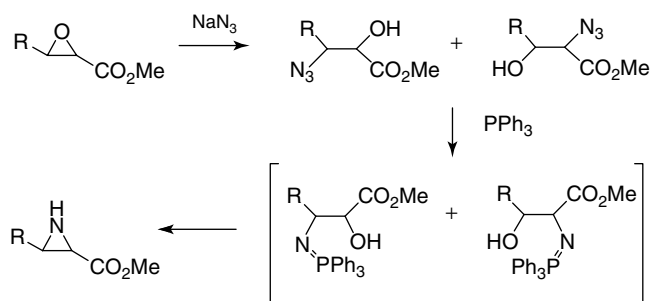
#### 1.1.4

#### Ring Transformation Methods

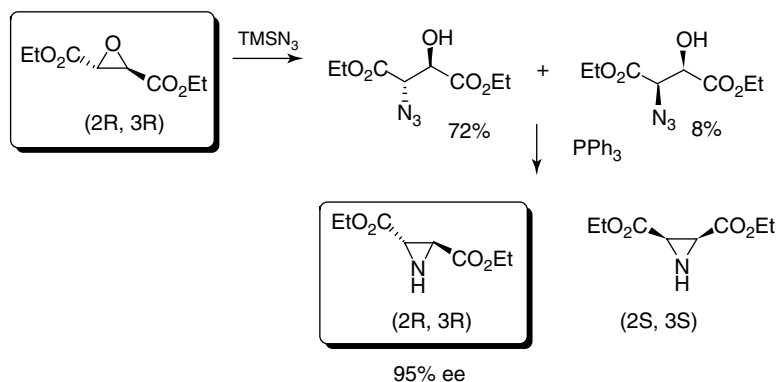
##### 1.1.4.1 Aziridines from Epoxides

The transformation of oxiranes to aziridines through a Staudinger-type reaction [70] represents a useful and well-known method for synthesis of these nitrogen-containing heterocycles.

The reaction occurs via the regioselective ring opening of the oxirane moiety by means of an azide followed by closure to aziridine by treatment with triphenylphosphine. Overall, both carbons of the initial epoxide are inverted.



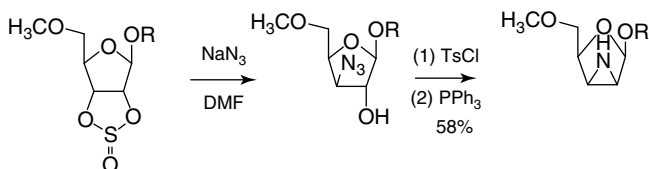
The absolute stereocontrol of this methodology suggests that starting from enantiopure oxiranes, enantiopure aziridines can be obtained. In particular, epoxides deriving from allylic alcohols, which are readily available in optically active form employing Sharpless epoxidation technique, can be considered excellent starting materials. The initial introduction of chirality may be guided by simple variation of the starting allylic alcohol (*Z* or *E*) and tartrate (*D* or *L*) geometries. The excellent regio- and stereospecificity of the following Staudinger reaction allows to obtain only one enantiomer of the aziridine by choosing the proper precursors. This methodology has been successfully applied to the preparation of aziridine-2-carboxylates [71], which represent an interesting class of compounds for their potential application as mimetics and precursors of both  $\alpha$ - and  $\beta$ -amino acids. In a similar way, the same authors applied this methodology to the preparation of enantiopure 2,3-dicarboxylic acid, the only example of naturally occurring aziridine-carboxylic acid, isolated as metabolite of *Streptomyces* MD398-A1 [72].



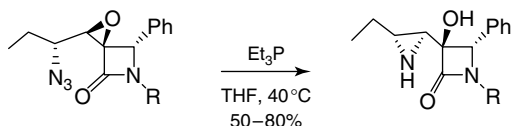
This methodology has been successfully applied to the preparation of building blocks for the synthesis of bioactive derivatives as carbapenems [73] or lipoxygenase pathway intermediates [74].

Enantiopure azides, useful starting material for the preparation of bicyclic analog of aziridine-2-carboxylates, have been obtained using readily available carbohydrates as a source of chirality. Thus, ring opening of 2,3-sulfite-furanoside by an azide group, followed by tosylation of the resulting hydroxyl moiety, gave

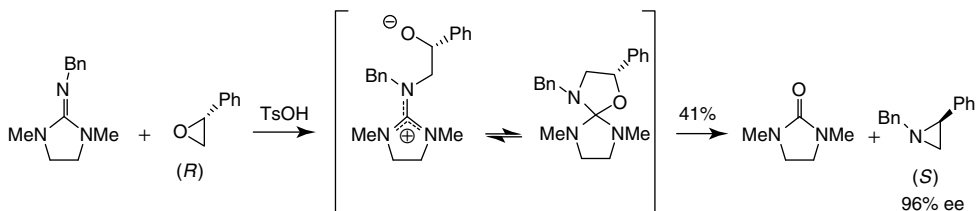
a reactive substrate for a Staudinger-type reaction, leading to carbohydrate-fused aziridines [75].



In general, the presence of an azido moiety vicinal to a good oxygenated leaving group is a sufficient requirement for the synthesis of aziridine rings via Staudinger-type mechanism. Recently, the preparation of polyfunctionalized azetidin-2-ones, bearing an aziridine ring and an hydroxyl moiety on the side chain, has been reported via aza-Payne displacement induced by triethylphosphine [76].

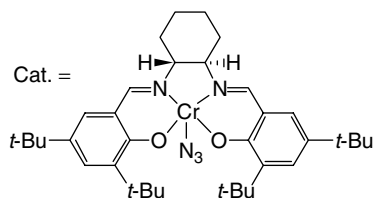
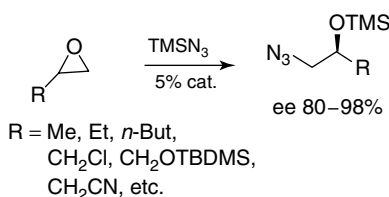
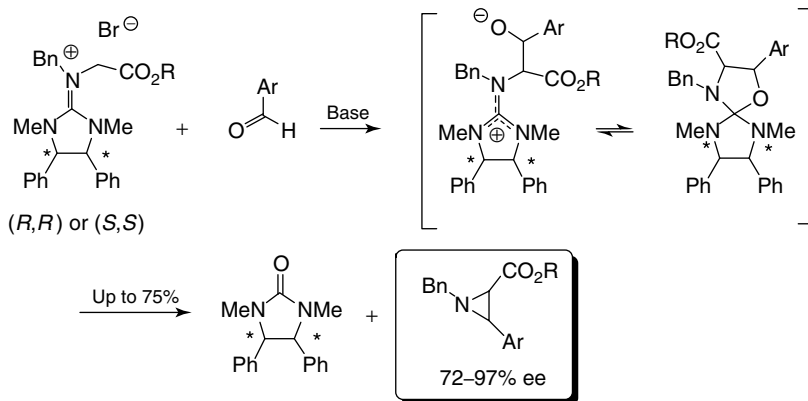


The direct conversion of chiral epoxides to aziridines can be also performed using a cyclic guanidine derivative as nitrogen source. The reaction involves the formation of a spiro intermediate, which undergoes acid catalysis fragmentation to aziridine and urea. Application of this procedure to (*R*)-styrene oxide gave (*S*)-aziridine in 41% yield [77].

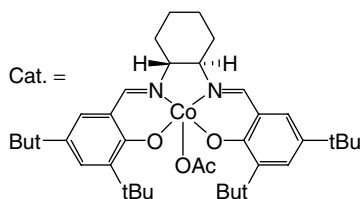
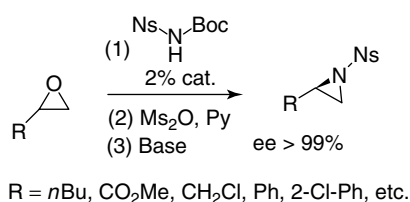


Following a very close mechanism, aziridine-2-esters have been obtained from enantiopure guanidine ylides and a variety of aryl aldehydes. This method afforded *trans*-aziridines as major diastereoisomers in excellent yields (up to 95%) and high enantiomeric excess (72–97%).

An efficient and practical route to enantiopure aminoalcohols starting from racemic terminal oxiranes via enantioselective ring opening with trimethylsilylazide in the presence of chromium-salen was presented by Jacobsen and coworkers. This kinetic resolution allowed the preparation of azido-alcohols with excellent enantiomeric excesses (80–98% ee) [78].



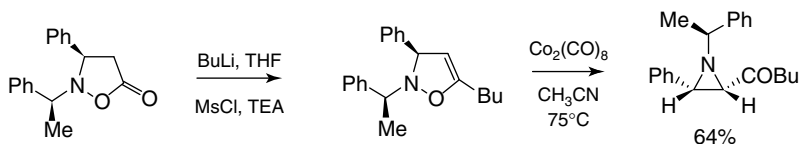
The same group explored the possibility to identify alternative nitrogen sources to overcome azide practical concerns and reported a general catalytic method for the preparation of enantiomerically enriched aziridines starting from racemic epoxides and *N*-Boc-2-nitrobenzenesulfonamide. The reaction, promoted by (S,S)-[(salen)Co-Ac], provided in few steps enantiopure *N*-nosylaziridines in yields ranging from 58 to 86% and enantiomeric excesses always higher than 99%. Moreover, the presence of the *N*-nosyl protecting group imparts to the heterocycle a particular reactivity toward nucleophilic addition [79].



#### 1.1.4.2 Aziridines from Other Heterocycles

4-Isoxazolines are useful synthons for the preparation of 2-acylaziridines through thermal rearrangement. This transformation was first reported by Baldwin and coworkers but its application to asymmetric synthetic purposes was scarcely developed. In order to accelerate this rearrangement, catalysts for N–O bond cleavage have been tested and  $\text{CO}_2(\text{CO})_8$  in anhydrous acetonitrile gave excellent

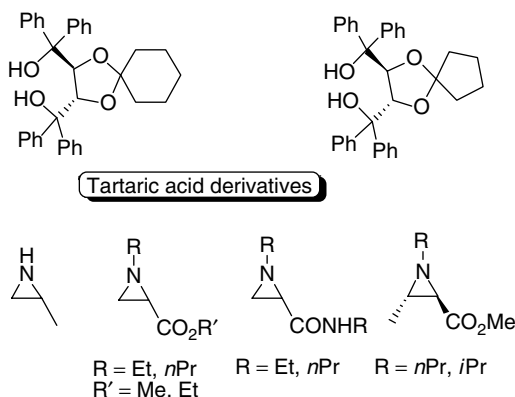
results. The transformation proceeds with complete diastereoselectivity when a stereogenic center is present in the substituent on the N atom [80].



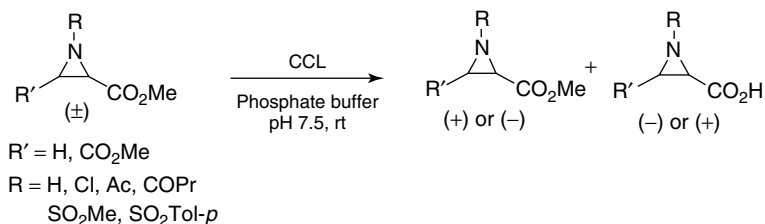
### 1.1.5

#### Racemate Resolution

Starting from racemic mixtures, mono- and disubstituted enantiomerically pure aziridines can be obtained by chemical or enzymatic resolution. Concerning chemical methods, an efficient resolution of *N*-alkyl-aziridine-2-carboxylates has been carried out by host–guest molecular association with optically active host compounds derived from tartaric acid [81].

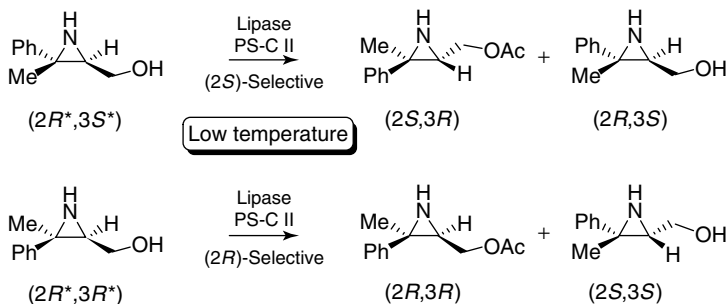


Efficient methods for the kinetic resolution of aziridines have also been obtained with the use of biocatalysts. Racemic substituted aziridine-methanol, aziridine-carboxylate, and aziridine-carboxamide derivatives have been easily separated. Enzymatic hydrolysis catalyzed by *Candida Cylindracea* Lipase (CCL) [82] has been performed both on *N*-unsubstituted aziridine-carboxylates and on more reactive *N*-chloro, *N*-acyl, or *N*-sulfonyl derivatives.

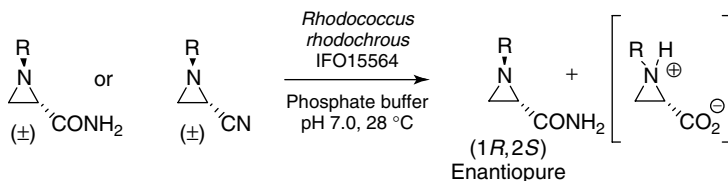




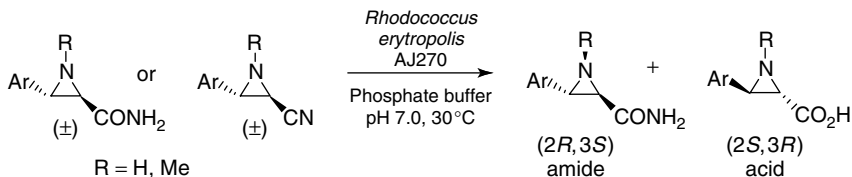
In a similar way Lipase PS-C II, immobilized on porous ceramic particles, has been reported to catalyze the resolution of  $(2R^*,3S^*)$  and  $(2R^*,3R^*)$ -3-methyl-3-phenyl-2-aziridinemethanol [83]. The temperature control on alcohol acetylation by means of vinylacetate suggests that enantioselectivity of this lipase-catalyzed kinetic resolution is favored by low temperature [84].



Biotransformation of racemic 1,2-*trans*-*N*-substituted-aziridine-2-carboxamides were carried out with a standard cell concentration of *Rhodococcus rhodochrous* IFO15564, an amidase-containing commercially available bacterium. Owing to the concomitant presence of a nitrile hydratase in these bacterial strains, the biotransformation was also successfully performed on *trans*-*N*-substituted-aziridine-2-carbonitriles [85].



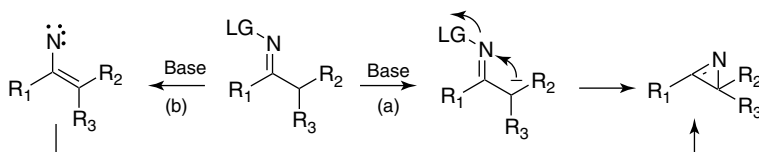
In a similar way, enantiopure  $(2R,3S)$ -3-aryl-aziridine-2-carboxamides were obtained from racemic 2,3-*trans*-aziridine-2-carbonitriles and amides under the catalysis of *Rhodococcus erythropolis* AJ270 whole cells. This highly efficient and enantioselective hydrolysis occurred under very mild conditions in aqueous phosphate buffer at pH 7.0 at 30 °C [86].



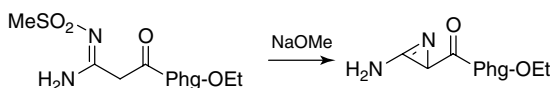
## 1.1.6

**Asymmetric Synthesis of Azirines****1.1.6.1 The Neber Reaction**

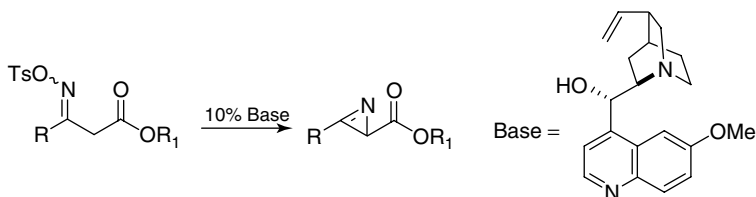
2H-Azirines have been first reported by Neber *et al.* in 1932 [87]. The Neber reaction possibly occurs either through an internal concerted nucleophilic displacement (route a) or via a electrocyclization of a vinylnitrene (route b), a reactive species formed by base-promoted loss of the leaving group on the nitrogen atom of oxime sulfonates and hydrazonium halides [88].



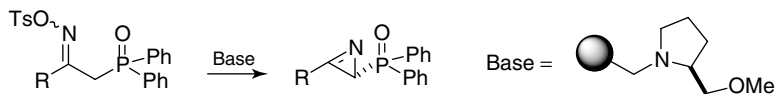
The first optically active 2H-azirine was synthesized by Neber reaction starting from the *O*-mesyl amidoxime derivative carrying a chiral phenylglycine (Phg) ester as a chiral auxiliary. Treatment of this derivative with base gave the 3-amino-2H-azirine in good yield and 96:4 stereoselectivity [89].



A remarkable asymmetric synthesis of azirine 2-carboxylates has been performed with a stoichiometric amount of dihydroquinidine or quinine as chiral tertiary base. The enantiomeric excess obtained ranged between 44 and 82%. Good results were also obtained when a catalytic amount (10 mol%) of quinidine was used. The hydroxy group of the base proved to be fundamental for a good stereoselectivity. Indeed, other chiral tertiary bases deprived of such hydroxy group, sparteine, brucine, and strychnine, did not provide any optically active azirine [90]. Later, this strategy has also been applied to the first synthesis of enantiomerically enriched 2-phosphinyl-2H-azirines [91].

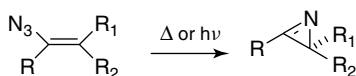


Finally, optically active 2H-azirines substituted in the 3-position with a phosphine oxide group or a phosphonate in the 2-position have been obtained with moderate enantiomeric excess by Neber reaction, starting from easily available oximes, and using chiral polymer-bound amines [92].

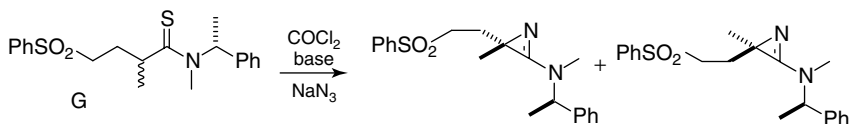


### 1.1.6.2 Thermal or Photochemical Treatment of Vinyl Azides

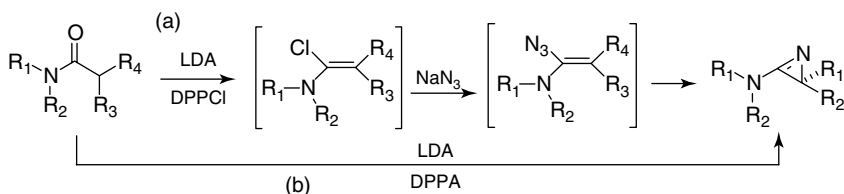
The thermal and/or photochemical treatment of vinyl azides has become a general method for the synthesis of 2H-azirines. In a similar way as for the Neber reaction,  $4\pi$ -electron vinylnitrenes are thought to be the intermediates, which would then undergo electrocyclicization to 2H-azirines.



Optically active 3-amino 2H-azirines can be obtained starting from mono- or disubstituted thioamides with a chiral substituent at the amino group, by treatment with phosgene/triethylamine and sodium azide [93]. This reaction is based on a previously reported synthetic protocol that likely proceeds through  $\alpha$ -chloro enamine and vinyl azide intermediates, which are not isolated [94].



The highly toxic phosgene can be substituted by diphenyl phosphorochloridate (DPPCl), (route a) [95]. Further, diphenyl phosphorazidate (DPPA) has been used as an alternative azide source allowing to obtain the azirines in a single step with very good yields (route b) [96].

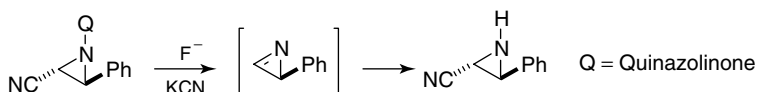


### 1.1.6.3 Elimination from Aziridines

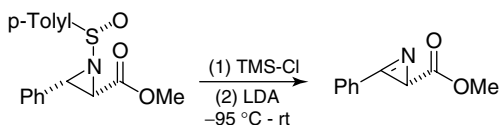
Aziridines carrying a leaving group at the nitrogen (*N*-chloro, *N*-sulfonyl, and *N*-acyl groups) are prone to elimination when treated with a base, giving 2H-azirines. This strategy has also been used for the asymmetric synthesis of azirine-carboxylates by the elimination of *N*-haloaziridines [97].



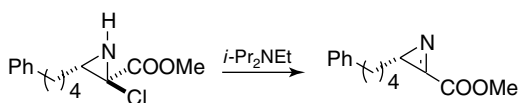
An alternative approach was based on the elimination of the  $\text{SiMe}_3$  and the *N*-quinazolinone substituents from a chiral aziridine promoted by cesium fluoride. The resulting optically active azirines were not isolated, but directly treated with nucleophiles to yield aziridines in high enantiomeric excess.



On the other hand, the treatment of chiral *N*-sulfinylaziridines with TMSCl followed by LDA gave 2H-azirine-2-carboxylates under complete regioselectivity. This procedure has been applied to the first asymmetric synthesis of the marine cytotoxic antibiotic (*R*)-(-)-dysidazirine and its (*S*)-(+)-epimer [98].

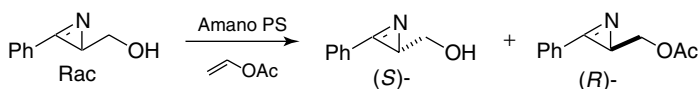


Most methods developed for the preparation of azirines cannot be utilized for the asymmetric synthesis of 2H-azirine-3-carboxylates. On the contrary, the dehydrochlorination of methyl 2-chloroaziridine 2-carboxylates provided the first examples of enantiopure 2-substituted 2H-azirine 3-carboxylates [99].



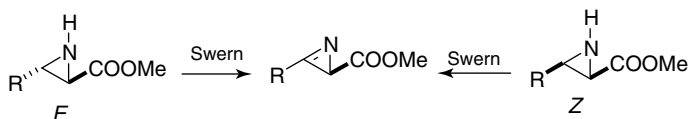
#### 1.1.6.4 Resolution of Racemic Azirines

Enantiomerically, pure 2H-azirines have been recently obtained by enzymatic methods. Thus, the kinetic resolution of the racemic 2H-azirinemethanol with Amano lipase at low temperature gave optically pure (*S*)-(1)-phenyl-2H-azirine-2-methanol and the (*R*)-(2)-acetate derivative [100].

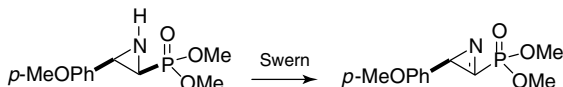


## 1.1.6.5 Oxidation of Aziridines

One of the first asymmetric syntheses of 2H-azirine-2-carboxylates described in the literature is the Swern oxidation of 3-alkylaziridine-2-carboxylates to the corresponding 2H-azirines. The oxidation of either the (*Z*) or the (*E*) isomers with  $\text{COCl}_2/\text{DMSO}$ , followed by  $\text{NEt}_3$ , proceeded with complete regioselectivity, in good yields and with retention of configuration of the surviving stereogenic center [101].



The Swern oxidation has been later utilized for the efficient synthesis of (+)-2H-azirine 3-phosphonate. This compound represents a new kind of chiral iminodienophile that on reaction with dienes such as trans-piperylene affords bicyclic aziridine adducts [102].



## 1.2

## Substituted Monocyclic Azetidines and Carbocyclic-Fused systems

## 1.2.1

## Generalities

Azetidines are four-membered nitrogen-containing analogs of cyclobutane whose nonplanar cyclic structure has been elucidated by electron diffraction and X-ray crystallographic studies.

Unsaturated derivatives of azetidine are also known as *1-azetines*, *2-azetines*, and *azetes*. Considerable attention has been paid in particular to the well-known amide derivatives azetidin-2-ones ( $\beta$ -lactams) that constitute systems of central importance due to their antibacterial properties. They have been the subject of many exhaustive reviews and books of bioorganic and medicinal chemistry owing to the widespread interest shown by scientists [103]. For this reason, in this chapter, their asymmetric synthesis are not treated. On the other hand, some azetidinones have been reported as starting materials for the preparation of enantiopure azetidines.



Azetidine



1-Azetine



2-Azetine



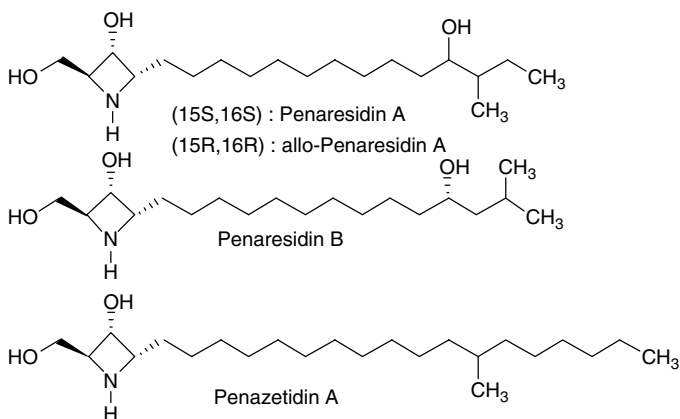
Azete

In comparison with strained highly reactive three-membered aziridines, the four-membered rings are more stable, unreactive toward reduction and susceptible of ring cleavage only at high temperature.

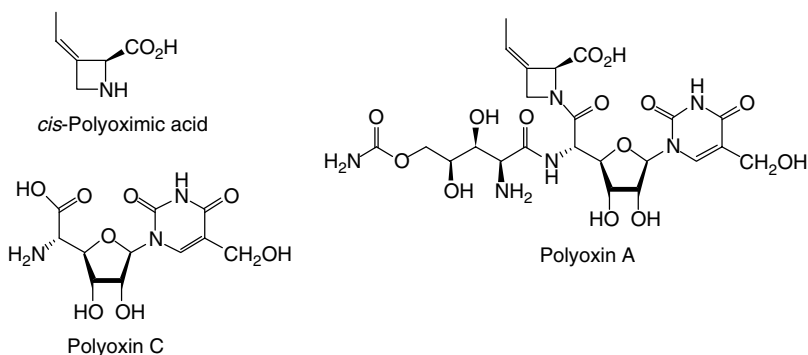
Nevertheless, azetidines are unstable toward mineral acids and ring cleavage by nucleophiles may be performed on protonated rings or in the presence of Lewis acid activation.

Azetidines are typical cyclic amines, appreciably more basic than both smaller and larger rings, showing in aqueous solution a  $pK_a = 11.29$ .

Naturally occurring azetidine derivatives are rare, and only in 1991 biologically active sphingosine-like compounds from marine origins, penaresidin A and B, were isolated as mixture of isomers. Tested as the mixture, they induced activation of myofibrils from rabbit skeletal muscle elevating the ATPase activity. After few years, a related compound, penazetidin A, was isolated from Indopacific marine sponge *Penares sollasi*, which possesses potent protein kinase C inhibitory activity.



The isolation and characterization of the polyoxin group nucleosides have been reported by Isono and coworkers [104]. Nucleoside polyoxins A, F, H, and K represent a class of antifungal antibiotics. An unusual common feature is the presence of an unsaturated azetidine-containing amino acid peptidically linked to polyoxin C.

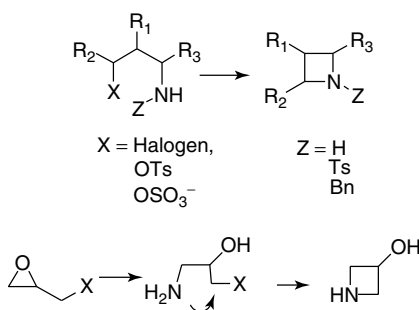


Finally, azetidine 2-carboxylic acids and 2-phosphonic acids have been recently proposed as conformationally constrained analogs of  $\alpha$ -amino acids in peptide chemistry [105]. Moreover, chiral  $C_2$ -symmetric 2,4-disubstituted azetidine derivatives showed excellent catalytic ability in the asymmetric addition of organozinc to carbonyl compounds.

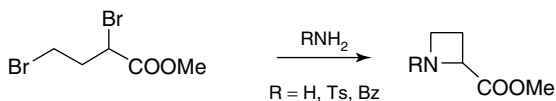
### 1.2.2

#### Cyclization Methods: Introduction

General synthetic methods for the preparation of azetidine ring are based on intramolecular displacement of a leaving group on carbon by a  $\gamma$ -amino function. Aminoalcohols and aminohalo-derivatives are among the most important classes of starting materials for heterocycle formation. Halo-alkyloxiranes have also been converted to 3-hydroxy-azetidines via epoxide ring opening by an amine followed by intramolecular nucleophilic displacement.



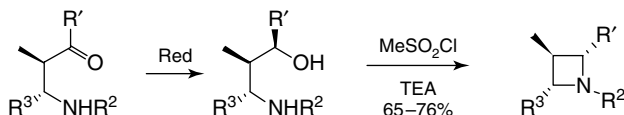
In a similar way, reaction of an amine or a sulfonamide with a 1,3-dihalogeno derivative results in the dialkylation of the nitrogen atom, providing a useful method for the preparation of NH, *N*-alkyl, or *N*-tosyl azetidines.



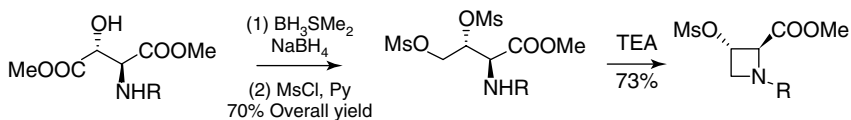
A general enantioselective synthesis of this class of four-membered rings is still lacking and the stereoselective methodologies presented so far suffer from indirect and lengthy procedures such as reduction of enatiopure  $\beta$ -lactams, bis-alkylation of 1,3-sulfonates with primary amines, or intramolecular *N*-alkylation involving 1,3-amino alcohols. Anyway, the transformation of these methodologies into asymmetric procedures has been performed mainly by cyclization of optically active precursors or by resolution of racemic azetidine mixtures. In the following sections, some selected examples are reported.

### 1.2.2.1 Cyclization methods: Enantiopure Azetidines via Formation of C–N Bond

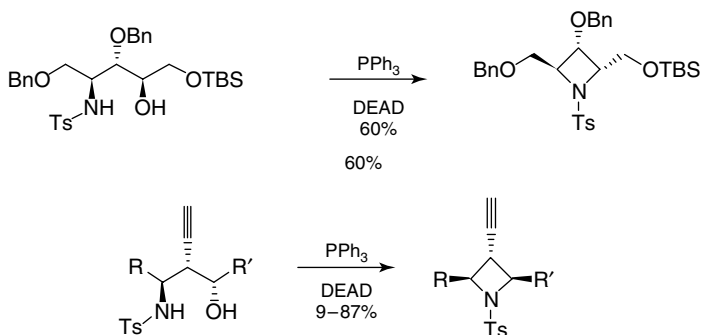
The most important and easy synthetic pathway to azetidines involves the ring closure of aminoalcohols induced by transformation of the hydroxyl moiety into a good leaving group. Many optically active amino alcohols are commercially available; nevertheless, they can also be easily obtained by asymmetric reduction of  $\beta$ -aminoketones or  $\beta$ -amino acids [106]. This approach has also been applied to the synthesis of bioactive alkaloids core and fused-azetidine rings present in bridged nucleosides [107].



When the reacting hydroxy derivative was obtained by reduction of hydroxyaspartate [108], the presence of two possible leaving groups generated a competition between three-membered and four-membered rings. A strong effect of the starting aminoalcohol stereochemistry on the regioselectivity of the process was demonstrated.



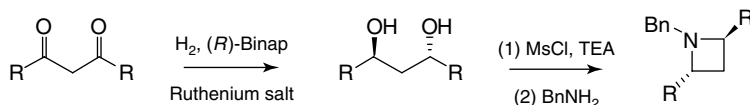
On polyfunctionalized amino alcohols, precursors of sphingosine-derived alkaloids named penaresidins, crucial cyclization has been induced under mild Mitsunobu conditions to yield enantiopure azetidines [109]. Under the same conditions, enantiopure ethynylazetidines were obtained in high yields from 2-ethynyl-1,3-aminoalcohols [110].



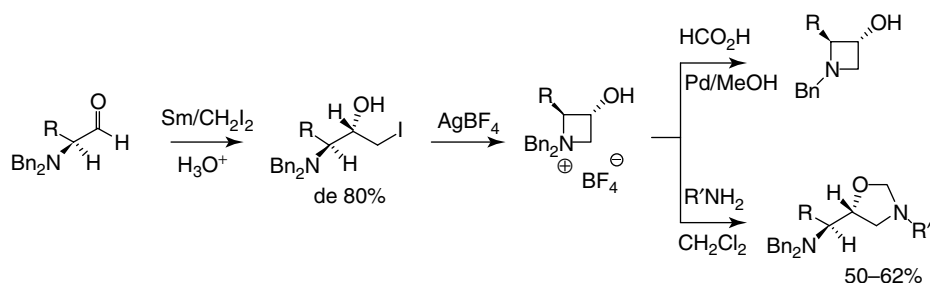
Enantiopure 1,3-diols, obtained by hydrogenation of 1,3-diketones in the presence of chiral ligands, have been successfully used as 2,4-disubstituted azetidine precursors. Treatment with methanesulfonyl chloride followed by reaction with an



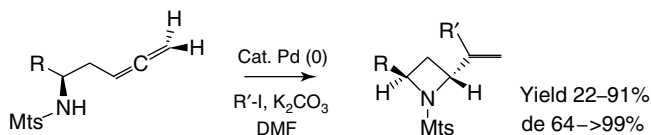
excess of benzylamine afforded *N*-benzyl heterocycles in yields ranging from 60 to 85% [111].



Iodomethylation of enantiopure  $\alpha$ -(dibenzyl)aminoaldehydes by means of samarium/diiodomethane under mild conditions gave optically active aminoiodohydrins, as precursors of azetidinium tetrafluoroborate salts. These salts are versatile building blocks that can be transformed into aminoepoxides, 1,3-oxazolidines, or turned into *N*-benzyl-hydroxyazetidines by simple hydrogenolysis [112].



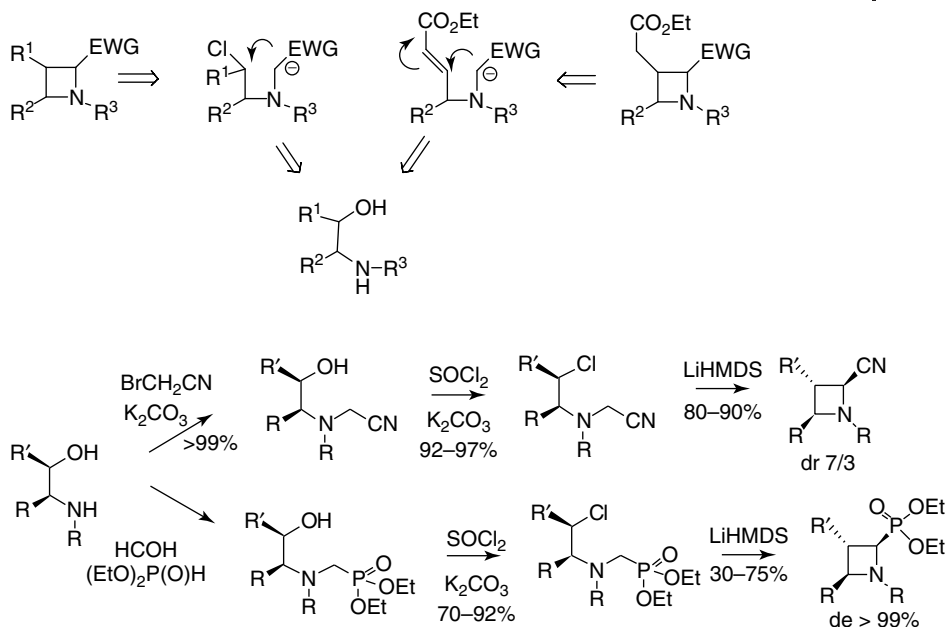
Ring closure of aminoallenes has attracted much attention in the development of stereoselective processes to five- or six-membered nitrogen-containing heterocycles. In a similar way, allenes bearing shorter carbon chain may lead to small size rings. Treatment of  $\beta$ -aminoallene and iodobenzene in the presence of palladium afforded exclusively 2,4-*cis*-azetidines in excellent yield [113].



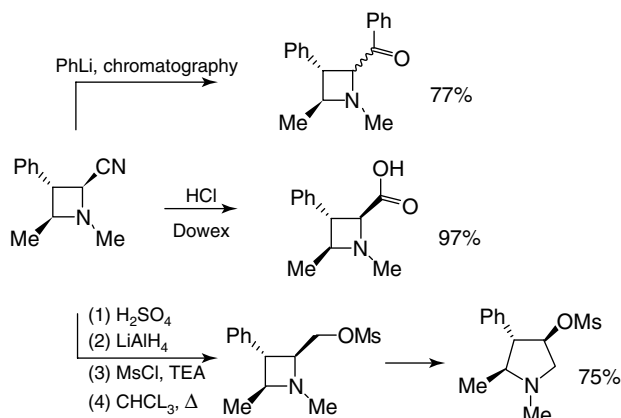
#### 1.2.2.2 Cyclization Methods: Enantiopure Azetidines via Formation of C–C Bond

Considerable attention has been paid to the synthesis of enantiopure azetidines bearing a nitrile or a phosphonic acid linked to the  $\alpha$  position of the ring, owing to the potential application of these molecules as precursors or mimics of cyclic amino acids. To this purpose, Couty and coworkers [114] developed an easy three-step methodology starting from readily available  $\beta$ -amino alcohols.

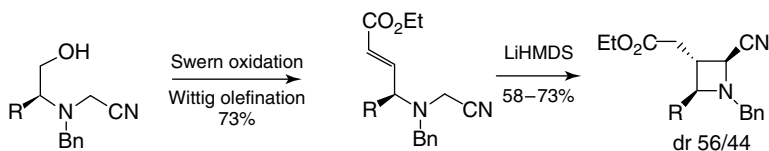
*N*-cyanomethylation or *N*-phosphomethylation of the starting material was followed by substitution of the alcoholic moiety by thionyl chloride. Stereoselective 4-*exo*-tet ring closure through intramolecular alkylation of the methylene group gave enantiopure azetidines.



2-Cyano azetidines are versatile building blocks that can be easily transformed into functionalized heterocycles. In fact, treatment of cyano azetidines with phenyllithium cleanly afforded 2-acyl azetidines. Unfortunately, under these conditions, complete epimerization at C2 could not be avoided. On the other hand, hydrolysis of the cyano derivatives into carboxylic acids required harsh conditions, and prolonged heating in concentrated acid was necessary to completely hydrolyze the intermediate amide. Although drastic conditions were applied, neither ring opening nor epimerization was observed. These derivatives were successfully introduced into peptidic sequences as constrained mimetics of natural amino acids. Finally, reduction of the nitrile to alcohol followed by mesylation allowed the expansion of enantiopure azetidines to 3-mesyloxy pyrrolidines.



Starting from the same *N*-cyanomethylated intermediates, the same authors reported the preparation of a new class of functionalized heterocycles via Wittig olefination of a transient amino-aldehyde followed by intramolecular Michael addition of the deprotonated methylene position. Unfortunately, low diastereoselectivity could be observed because of the base-catalyzed equilibration between stereoisomers [115].

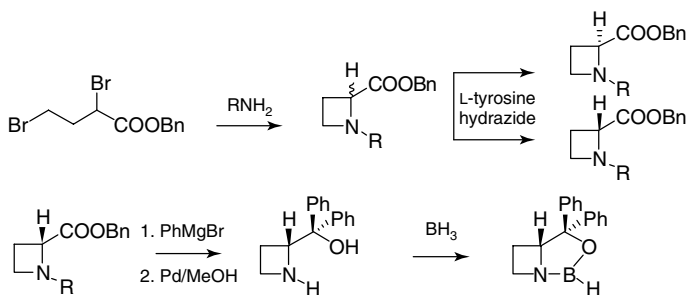


### 1.2.3

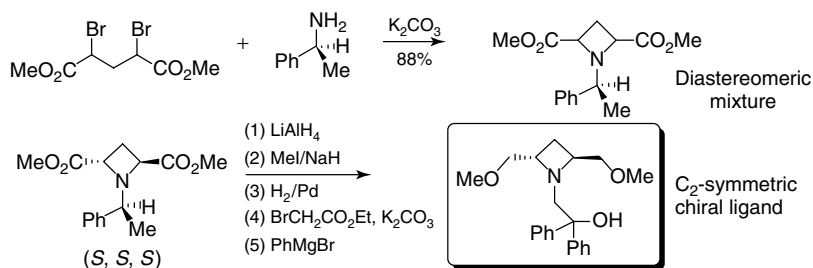
#### Azetidines by Resolution of Racemates

Azetidines can be obtained in enantiomerically pure form through enzymatic or chemical resolution of racemic mixtures.

Starting from the Baldwin's adaptation of Cromwell general method of preparation of azetidine from 1,3-dihalogeno compounds, racemic azetidine-2-carboxylates were obtained in 96% by reaction with benzhydramine under microwave irradiation in  $\text{CH}_3\text{CN}$ . The resolution [116] was conveniently carried out by using *L*-tyrosine hydrazide as a resolving agent. Enantiomerically pure azetidines have been converted into (*R*)- or (*S*)-oxazaborolines, useful for the enantioselective reduction of prochiral ketones.

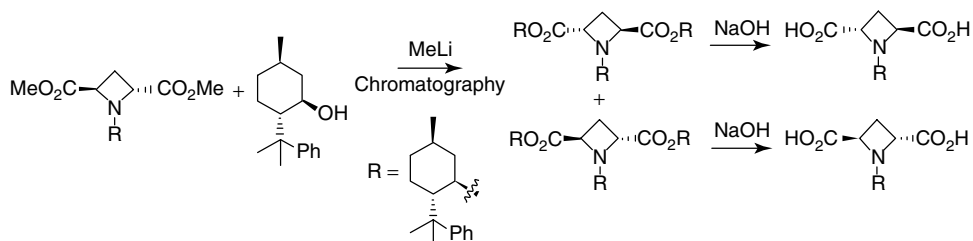


(*S*)-1-Phenylethylamine has been used as a chiral auxiliary as well as a nitrogen atom donor in the synthesis of an enantiomeric pair of azetidine-2,4-dicarboxylic acids from racemic dibromoderivatives; the absolute configuration of one of which has been assigned on the basis of the X-ray structure and the known absolute configuration of the (*S*)-1-phenylethylamine moiety [117]. These  $C_2$ -symmetric disubstituted heterocycles have been successfully exploited as rigid core for the preparation of chiral ligands in the asymmetric addition of diethylzinc to aldehydes.

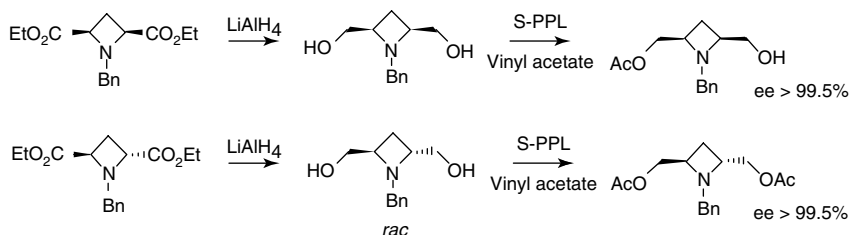


The application of hydroxy-azetidines as chiral ligands for zinc-catalyzed enantioselective additions was also previously reported by Martens and coworkers. Starting from (S)-azetidinecarboxylic acid, a constituent of the natural mugineic acid and one of the few commercially available azetidines, the chiral catalyst was prepared by enantioselective catalytic reduction of ketone moiety in the presence of oxazaborolidines [118].

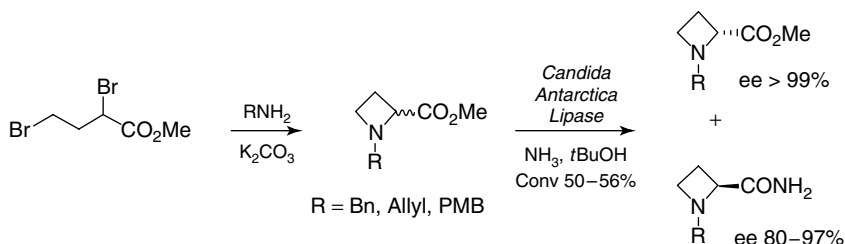
Resolution of racemic *trans*-azetidine-2,4-dicarboxylic acids, synthesized following the same procedure, was achieved by transesterification of N-substituted dimethylesters with (-)-8-phenylmenthol and chromatographic separation of the resulting diastereoisomers [119].



Starting from dicarboxylic derivatives, *cis*- and *trans*-dihydroxy-substituted heterocycles were obtained by reduction with  $LiAlH_4$ , followed by treatment with benzylamine. The dihydroxy-meso compound was desymmetrized and transformed into monoacetate by the immobilized mammalian lipase from *Porcine pancreas* (S-PPL). The best results were obtained when diisopropylether was used as co-solvent in the presence of vinyl acetate. Optimized procedure allowed to obtain enantiomeric excess higher than 98% by stopping the reaction at conversion around 55%. Longer reaction times showed the formation of a significant amount of *meso*-diacetate derivative. Using the same enzyme, the *trans* isomer was resolved by a double kinetic resolution, stopping the reaction at moderate degree of conversion. In this case, the diacetate was isolated by the higher enantiomeric excess, while the starting dihydroxyderivative was isolated with 94.5% ee after recrystallization [120].



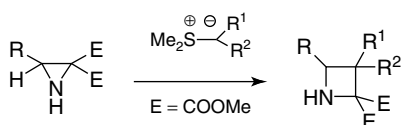
Enzymatic resolution of *N*-alkyl-azetidine-2-carboxylates could be accomplished via transacylation of ammonia catalyzed by *Candida Antarctica* lipase. Treatment of racemic azetidine-esters with an alcoholic saturated solution of ammonia afforded enantiopure unreacted (*R*)-esters and highly enriched (*S*) amides [121].



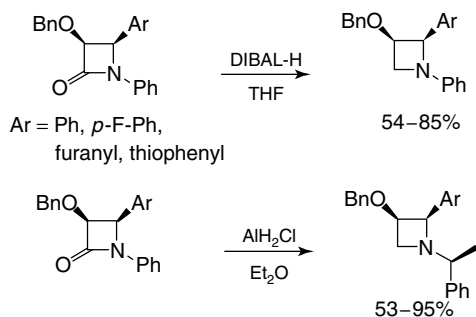
#### 1.2.4

##### Azetidines by Ring Transformation

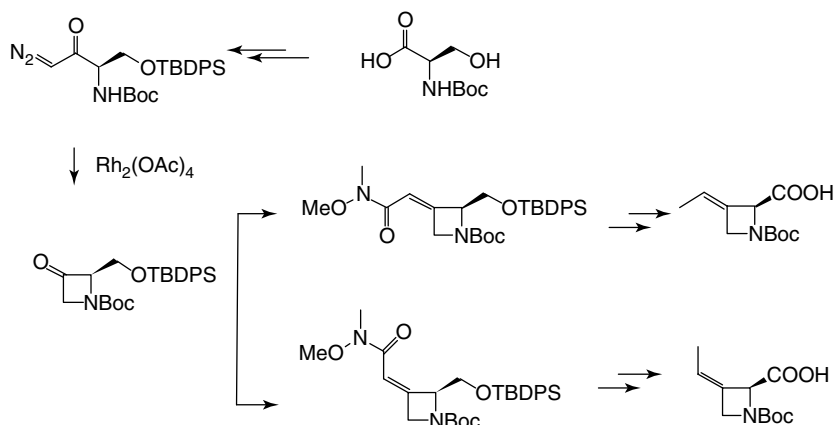
Transformation of heterocyclic precursors represents a further possibility for the synthesis of this class of compounds. One of the most important features is the ring expansion of activated aziridines.



Azetidine derivatives carrying a carbonyl group on the ring backbone occupy a special place in heterocyclic chemistry. Besides the well-known natural and synthetic azetidin-2-one derivatives, whose asymmetric synthesis has been extensively reviewed in the past, much less attention has been paid to azetidin-3-ones. Recently, a useful protocol for the synthesis of these heterocycles has been reported by De Kimpe and coworkers [122], starting from readily accessible *N*-alkylidene-tribromopropylamines. Anyway, both classes of compounds represent starting materials for the preparation of azetidine derivatives. Optimization of the conditions for chiral nonracemic azetidinones reduction with metal hydrides allowed to identify DIBAL-H or  $\text{AlH}_2\text{Cl}$  as the reagents of choice [123].



Natural-cis and unnatural-trans polyoximic acids have been synthesized starting from D-serine through 1-3-azetidinone-2-hydroxymethyl chiron using a rhodium-mediated diazoketene insertion reaction. By choosing the proper reagents, the following Horner-Wadsworth-Emmons and Wittig reactions were suited to exclusively obtain the cis or the trans isomer [124].



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## 2

## Asymmetric Synthesis of Five-Membered Ring Heterocycles

Pei-Qiang Huang

### 2.1

#### Monocyclic Pyrrolidines and Pyrrolidinones

#### 2.1.1

##### Generalities

The pyrrolidine structural unit is one of the most commonly occurring structural cores in a large number of biologically active alkaloids [1]. For example, since its first isolation in 1954 [2a], anisomycin (**1**) has become a valuable tool in molecular biology, having been used for the treatment of *Trichomonas vaginitis* and amoebic dysentery, and also as an agricultural fungicide. Recent investigation showed that anisomycin and its higher homolog 3097-B1 (**1a**) as well as 3097-B2 and 3097-C2 exhibited *in vitro* anticytotoxic activity (Figure 2.1) [2b]. The role of the naturally occurring excitatory amino acid (*R*)- $\alpha$ -kainic acid (**2**) in mediating synaptic responses has made it an important reagent for investigations into Alzheimer's disease, epilepsy, and other neurological disorders [3]. It has also been used as an antiworming agent to eliminate parasites from humans and animals. (+)-Lactacystin (**3**) is a potent and selective proteasome inhibitor that was isolated from *Streptomyces* sp [4]. Recently, a more potent proteasome inhibitor, (–)-salinosporamide A (**4**), was isolated from a marine actinomycete [5] and it inhibits proteasomal proteolytic activity with an  $IC_{50}$  value of 1.3 nM. Moreover, compound **4** has potent *in vitro* cytotoxicity ( $LC_{50} < 10$  nM against four different cancer cell lines).

On the other hand, pyrrolidine is also a motif for designing pharmaceuticals. For example, nemonapride (YM-09151-2) (**5**) was marketed in 1991 as a potent antipsychotic drug [6]. Recently, A-315675 (**6**) was developed by scientists at Abbott laboratories as a potent influenza neuraminidase inhibitor and is a candidate for development as an anti-influenza drug [7].

In addition to their underexplored medicinal importance, functionalized pyrrolidines have found wide applications as chiral ligands [8], chiral auxiliaries [9], and organocatalysts [10] in asymmetric synthesis.

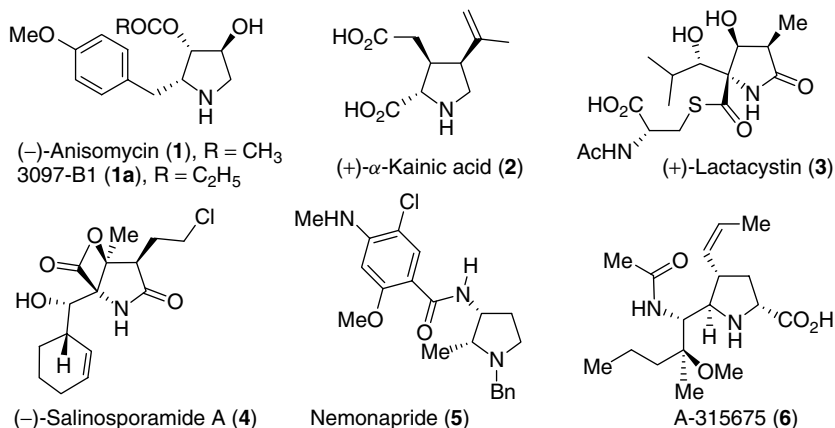


Fig. 2.1 Selected examples of bioactive pyrrolidines/pyrrolidin-2-ones.

Consequently, significant efforts have been devoted to the development of efficient routes to substituted pyrrolidines.

### 2.1.2

#### Cyclization Methods

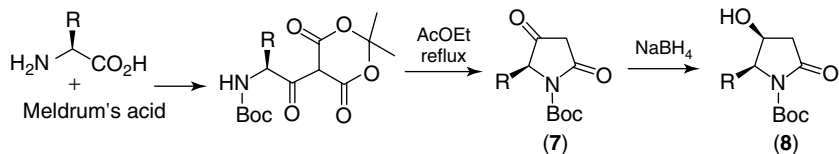
Formation of the pyrrolidine/pyrrolidinone ring by cyclization is a widely used approach. Almost all disconnections around pyrrolidine/pyrrolidine-2-one ring are viable, including  $\text{C}_1/\text{C}_5\text{-N}$  bond,  $\text{C}_2\text{-C}_3$  bond, and  $\text{C}_3\text{-C}_4$  bond disconnections, as well as  $\text{C}_1\text{-N}/\text{C}_5\text{-N}$  double disconnections.

##### 2.1.2.1 Cyclization via $\text{C}_1/\text{C}_5\text{-N}$ Bond Formation

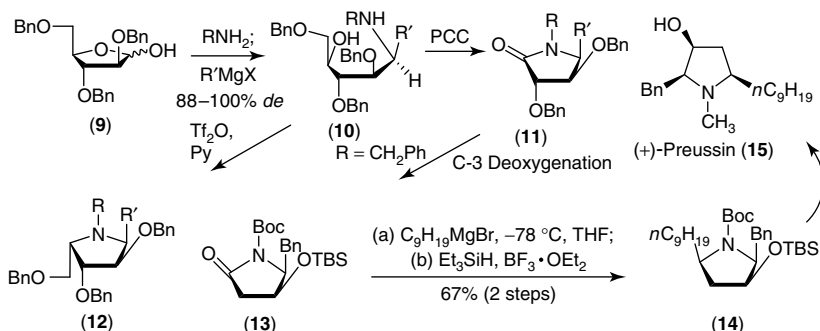
Many methods have been reported for the synthesis of pyrrolidines and pyrrolidin-2-ones by intramolecular amination or amidation of chiral nonracemic alicyclic amines or amides. They will be classified according to the methods used to synthesize the chiral nonracemic alicyclic precursors.

**Naturally Occurring Chiron Approach** Enantiomerically pure  $\alpha$ -amino acids are cheap and easily available chirons [11]. A three-step synthesis of 5-alkyltetramic acids **7**, developed by Jouin and Castro [12], provides a flexible approach to *cis*-4-hydroxy-5-alkylpyrrolidin-2-ones **8** after a highly stereoselective reduction with  $\text{NaBH}_4$ , and to 2,5-disubstituted pyrrolidin-4-ols after further transformations (Scheme 2.1).

Sugars provide a rich source of chirons for the synthesis of enantiomeric pure hydroxylated pyrrolidines/pyrrolidin-2-ones. Nicotra developed a four-step method for the synthesis of 4,5-*cis*-substituted pyrrolidine-2-ones (**11**) and pyrrolidines (**12**) starting from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**9**) (Scheme 2.2) [13]. This provided a basis for the asymmetric synthesis of antibiotic anisomycin (**1**) [14a] and the antifungal agent (+)-preussin (**15**) [14b], as well as pyrrolizidine alkaloid



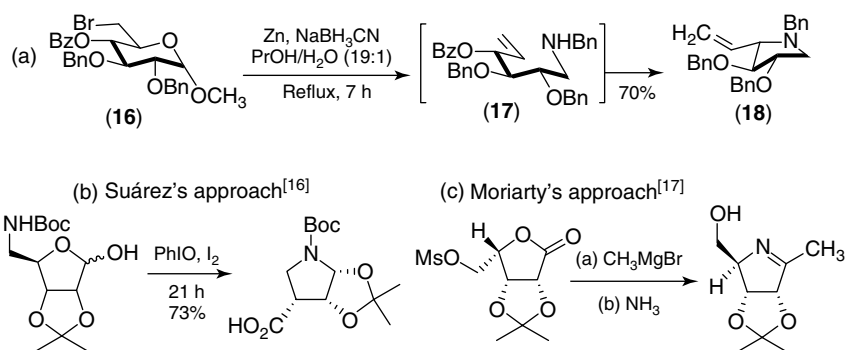
**Scheme 2.1** An  $\alpha$ -amino acid-based approach to tetramic acids and *cis*-4-hydroxy-5-alkylpyrrolidin-2-ones.



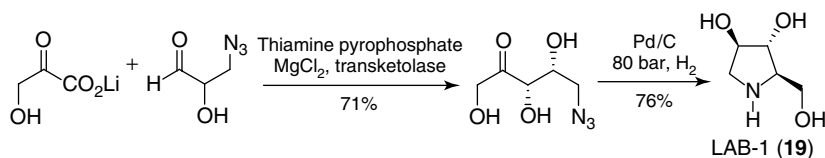
**Scheme 2.2** Nicotra's approach to hydroxylated pyrrolidin-2-ones/pyrrolidines (TBS = *tert*-butyl-dimethylsilyl).

(+)-alexine [14c]. To introduce the C-5 side chain of (+)-preussin, Yoda *et al.* developed a reductive alkylation method ( $13 \rightarrow 14$ ), which allows the establishment of C<sub>2</sub>/C<sub>5</sub> *cis* stereochemistry with high diastereoselectivity [14d,e].

Scheme 2.3 shows three approaches for the rapid transformation of sugars into pyrrolidine/1-pyrroline derivatives [15–17]. In Ganem's approach (Scheme 2.3a) [15], upon treatment of bromobenzoate **16** with Zn-NaBH<sub>3</sub>CN, reductive ring opening and reductive amination occurred to give **17**, which was followed by a spontaneous intramolecular displacement of the benzoate in **17**, leading to pyrrolidine **18** in 70% yield from **16**.



**Scheme 2.3** Three rapid approaches for the transformation of sugars to pyrrolidine/1-pyrroline derivatives.



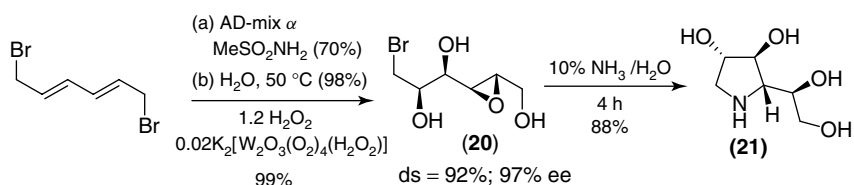
**Scheme 2.4** Enzymatic synthesis of azasugar LAB-1.

**Enzymatic Approach** Among various routes to azasugars, an enzymatic route should be quite efficient, because such approaches are generally free of deprotection–protection procedures. Effenberger *et al.* developed an enzymatic synthesis of 5-azido-5-deoxy-D-xylose, which led to the synthesis of azasugar LAB-1 (**19**, Scheme 2.4) [18]. Wong *et al.* undertook a systematic study on chemo-enzymatic synthesis, which led to the synthesis of many polyhydroxylated pyrrolidines [19].

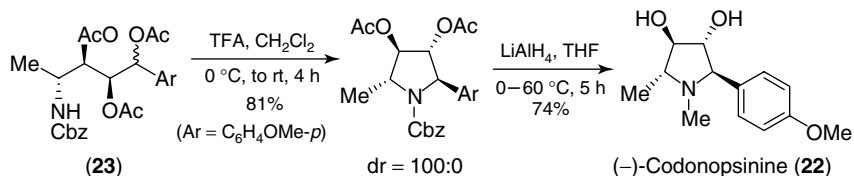
**Catalytic Asymmetric and Chiral Auxiliary-Induced Approaches** The efficient enantioselective synthesis of polyhydroxypyrrolidine **21** shown in Scheme 2.5 involves a sequential Sharpless asymmetric dihydroxylation and asymmetric epoxidation in the presence of the Mizuno's dinuclear peroxotungstate catalyst. Final treatment of **20** with 10% NH<sub>3</sub> in water gave azasugar **21** in 88% yield [20] via a tandem nucleophilic substitution–intramolecular ring opening of the epoxide.

A recent synthesis of (–)-codonopsinine (**22**) illustrates a new approach to substituted pyrrolidines. It involves a highly *trans*-diastereoselective intramolecular S<sub>N</sub>1 reaction via a resonance-stabilized benzylic carbocation intermediate derived from **23**, which was synthesized via the Sharpless asymmetric dihydroxylation reaction (dr = 91:9) (Scheme 2.6) [21].

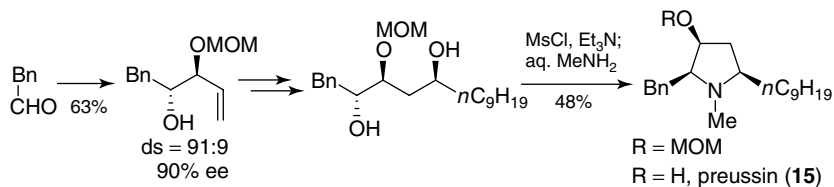
On the basis of iterative asymmetric Ti-mediated allylations, Cossy and coworkers developed an asymmetric approach to (+)-preussin (**15**). The two titanium-complex-



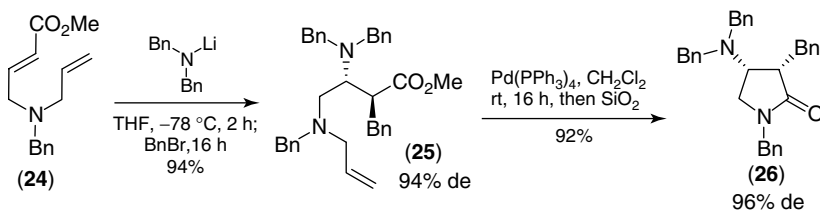
**Scheme 2.5** A concise enantioselective synthesis of polyhydroxypyrrolidine.



**Scheme 2.6** Rao's enantioselective synthesis of polyhydroxypyrrolidine.



**Scheme 2.7** Cossy's Ti-mediated asymmetric allylation approach to (+)-preussin.



**Scheme 2.8** Davies' diastereoselective approach to 3-substituted 4-aminopyrrolidines.

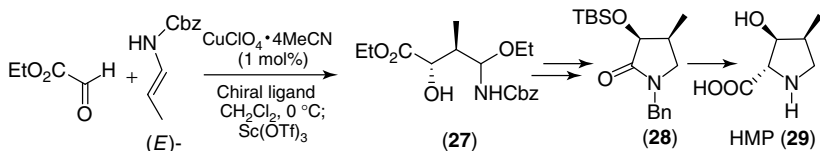
catalyzed asymmetric allylation reactions proceeded with 91:9 and 96:4 diastereoselectivities respectively, which established all three stereogenic centers of the target molecule (Scheme 2.7) [22].

As an application of their chiral lithium amide conjugate addition methodology (24 → 25), Davies *et al.* developed a highly diastereoselective and enantioselective approach to 3,4-*trans*- and 3,4-*cis*-substituted aminopyrrolidines (Scheme 2.8) [23].

Catalytic enantioselective and diastereoselective addition of enecarbamates with  $\alpha$ -oxo aldehydes provides a one-step synthesis of  $\gamma$ -amino acid derivative 27, which was converted subsequently into substituted 3-hydroxypyrrolidin-2-one 28 and 3-hydroxy-4-methylproline (HMP, 29, Scheme 2.9) [24].

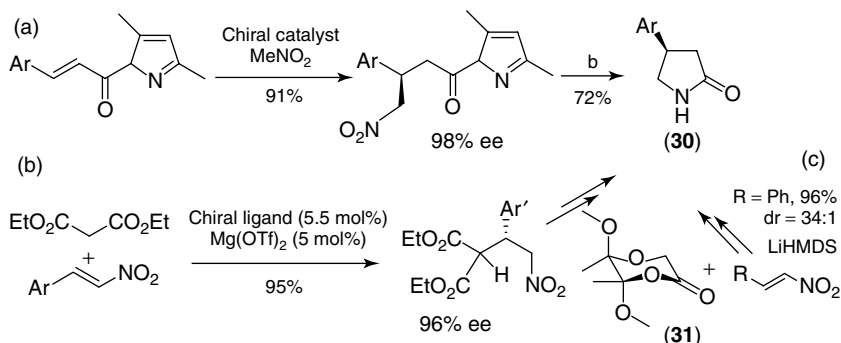
Recently, two catalytic enantioselective Michael addition-based approaches to  $\beta$ -aryl- $\gamma$ -lactams 30 have been developed by Kanemasan [25] and Barnes [26] (Scheme 2.10a and b respectively), with the latter being used in the synthesis of the antidepressant rolipram. The same product can also be obtained via Ley's butane-2,3-diacetal (BDA) derivative 31-based Michael addition (Scheme 2.10c) [27].

In Shibasaki's catalytic asymmetric total synthesis of (+)-lactacystin, the lactam intermediate 32 was made by subsequent oxidative cleavage, oxidation, and lactamization of the chiral cyclopentene derivative 33, obtained via an enantioselective Strecker reaction of ketoimine 34 (Scheme 2.11) [28].

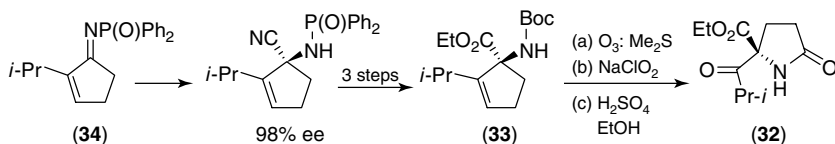


**Scheme 2.9** Enantioselective Stork-type approach to substituted 3-hydroxypyrrolidin-2-one.

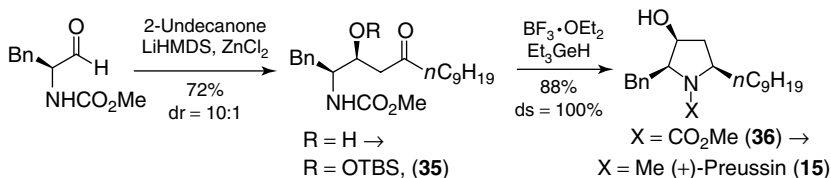




**Scheme 2.10** Three enantioselective approaches to  $\beta$ -aryl- $\gamma$ -lactams.



**Scheme 2.11** Shibasaki's catalytic asymmetric approach to (+)-lactacystin.

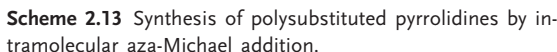


**Scheme 2.12** Kitahara's intramolecular reductive amidoalkylation approach to (+)-preussin.

A combination of chelation-controlled *syn*-selective aldol reaction of  $\alpha$ -amino aldehyde and zinc enolate of 2-undecanone, with Lewis acid-promoted intramolecular reductive amidoalkylation ( $35 \rightarrow 36$ ), establishes a concise and highly diastereoselective approach to (+)-preussin (15) (Scheme 2.12) [29].

Synthesis of substituted pyrrolidines by both substrate [30] and chiral auxiliary [31]-induced asymmetric intramolecular aza-Michael addition was reported. As shown in Scheme 2.13, reaction of hemiaminal 37 with the carbanion generated from trimethyl phosphonoacetate led, via a tandem Wittig-aza-Michael reaction, to the formation of all-*cis*-trisubstituted pyrrolidine 38 in 5.6:1 diastereoselectivity [30]. Remarkably, starting from methylated hemiaminal 40, all-*cis*-tetrasubstituted pyrrolidine 41 was formed as a single diastereomer in 75% yield.

Metal and halogen-mediated intramolecular cyclizations of amido/amino-olefins/allenes/alkynes constitute another versatile strategy for pyrrolidine formation.  $\text{Pd}(0)$  complex,  $\text{Hg}(\text{II})$  salt, and  $\text{Ag}(\text{I})$  salt are the most frequently used metal catalysts.



The concise five-step synthesis of the antifungal agent (+)-preussin (**15**) is an excellent demonstration of the power of Hg(II)-mediated ring closure of ynone **45** (Scheme 2.15) [35].

(43)

$\xrightarrow[\text{NaHCO}_3, \text{KBr}]{\text{Hg(OAc)}_2}$

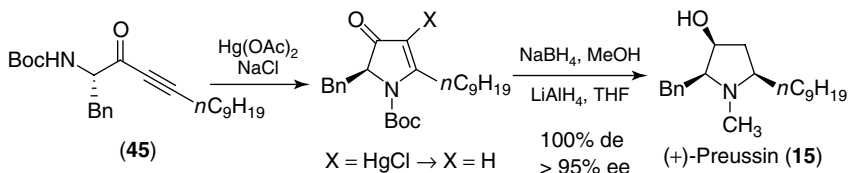
dr > 15:1

$\xrightarrow[\text{DMF}]{\text{O}_2, \text{NaBH}_4}$

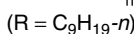
44% (two steps)

(44a) X = OH  
 (44b) X = H

**Scheme 2.14** Han's asymmetric synthesis of azasugars by mercury(II)-mediated amidomercuration.



**Scheme 2.15** Hecht's Hg(II)-mediated ring closure approach to (+)-preussin.



to preussin and Pd(0)-catalyzed amidation of allylic epoxide.

in 90:10 ratio (Scheme 2.16b) [37].

diastereoselection.

(Scheme 2.18).

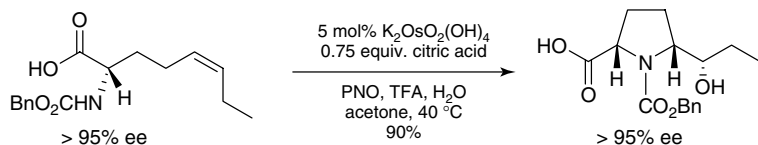
(Scheme 2.19) [41].

aziridinol **55** in high *syn*-selectivity. Treatment of the *syn*-aziridinol **55** with base led,

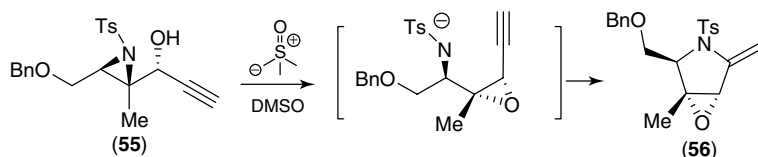


**Scheme 2.17** Intramolecular iodosulfonamidation approach to 2,5-*trans*-pyrrolidines.

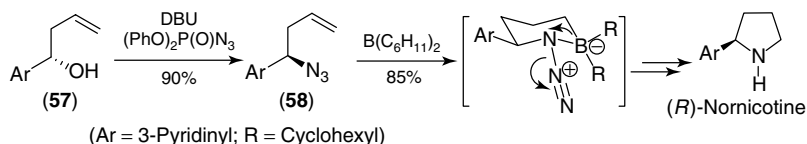
**Scheme 2.18** Park's approach to anisomycin (PMP = *para*-methoxyphenyl).



**Scheme 2.19** Synthesis of *cis*-2,5-disubstituted pyrrolidines by osmium-catalyzed oxidative cyclization of aminoalkenes.



**Scheme 2.20** Borhan's tandem aza-Payne/hydroamination reaction-based approach to tetrasubstituted pyrrolidines.



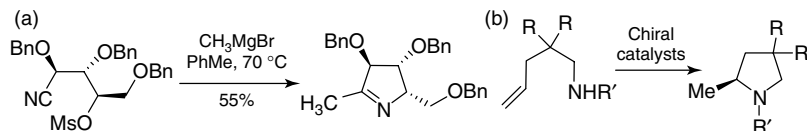
**Scheme 2.21** Synthesis of pyrrolidines by intramolecular hydroboration-cycloalkylation.

via successive aza-Payne rearrangement and hydroamination, to epoxypyrrolidine 56 (Scheme 2.20) [42].

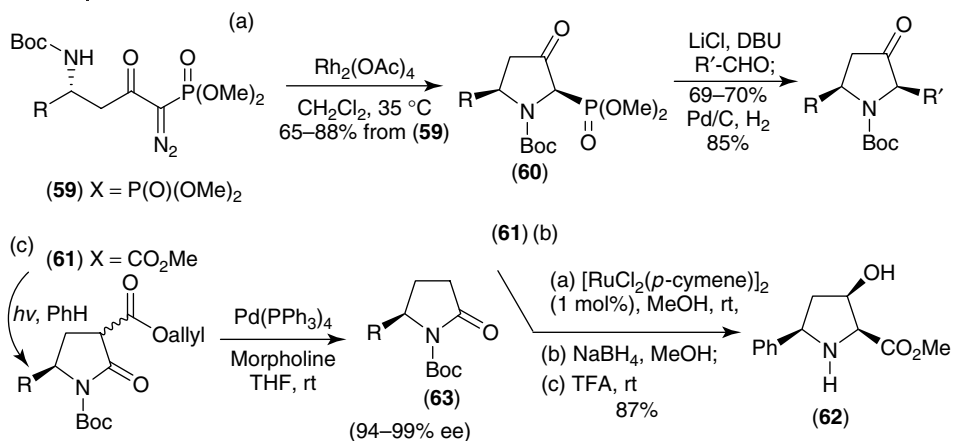
The intramolecular hydroboration-cycloalkylation of azido-olefins affords an attractive method for the synthesis of pyrrolidines [43, 44] because of the easy availability of the precursor. As shown in Scheme 2.21, the unnatural (*R*)-nicotine was synthesized in four steps with an overall yield of 51%. The starting (*S*)-homoallylic alcohol was obtained in 86% yield with 94% ee by asymmetric allylation.

Scheme 2.22a shows a general method for the synthesis of ketimine-type iminosugars, based on the tandem Grignard reagent addition/cyclization reaction of methanesulfonyl glyconitriles, which are easily available from sugars [45].

In recent years, several catalytic asymmetric hydroamination methods have been developed. For example, chiral phosphoric acid diesters [46] and binaphthylamido ytterbium ate complexes [47] were shown to be effective catalysts for the intramolecular hydroaminations of nonactivated alkenes (Scheme 2.22b).



**Scheme 2.22** Synthesis of ketimine-type iminosugars and catalytic asymmetric intramolecular hydroamination.

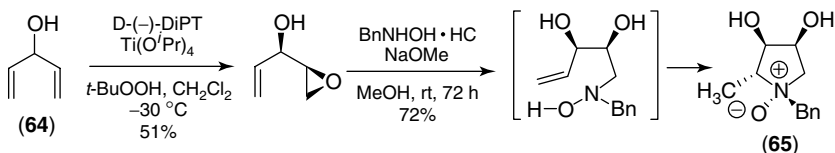


**Scheme 2.23** Synthesis of 3-oxopyrrolidines via N–H insertion and 2-oxopyrrolidines via the Wolff rearrangement.

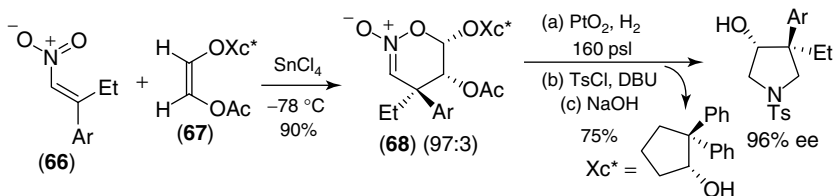
Metal carbenoid N–H insertion constitutes a particular method for the formation of 3-oxopyrrolidine rings (Scheme 2.23). Treatment of the  $\alpha$ -diazo compound **59** with 4 mol% of  $Rh_2(OAc)_4$  resulted in the formation of 3-oxopyrrolidine phosphate **60**, which can be converted into *cis*-2,5-disubstituted 3-oxopyrrolidines, and *cis*-2,5-disubstituted pyrrolidines (Scheme 2.23a) [48]. Che reported that  $[RuCl_2(p\text{-cymene})_2]$  is also an effective catalyst for the N–H insertion reaction which, in tandem with sodium borohydride reduction, afforded 5-substituted 3-hydroxyprolinates **62** with good chemical yield and stereoselectivity (Scheme 2.23b) [49]. Wang *et al.* showed that the reactions of  $\alpha$ -diazo compound **61** can lead to either 2-oxo or 3-oxo-pyrrolidine derivatives (Scheme 2.23c) [50]. Under photoinduced conditions, a Wolff rearrangement reaction occurred, leading to the formation of 2-oxopyrrolidine derivatives (**63**) after subsequent decarboxylation.

Divinylcarbinol **64** is a usual prochiral building block for the asymmetric synthesis of pyrrolidines via Sharpless asymmetric epoxidation [51–53]. Aminolysis followed by the reverse-Cope cyclization [54] afford an easy access to substituted pyrrolidine N-oxides **65** (Scheme 2.24) [53].

Denmark developed a chiral auxiliary-induced regioselective asymmetric [4 + 2] cycloaddition of 2-(acetoxyl)vinyl ethers with nitroalkenes, which provides an efficient approach to pyrrolidines with a quaternary chiral center (Scheme 2.25) [55a]. Extension of this strategy to asymmetric tandem [4 + 2]/[3 + 2] cycloadditions



**Scheme 2.24** Synthesis of substituted pyrrolidine N-oxides by the reverse-Cope cyclization.



**Scheme 2.25** Denmark's approach to 3-hydroxypyrrolidines.  
Ar = 3,4-dimethoxyphenyl; Ac = acetyl; Ts = *p*-toluenesulfonyl.

provides a powerful methodology for the synthesis of pyrrolizidine alkaloids such as (+)-macronecine, (+)-petasinecine, and (–)-hastanecine [55b].

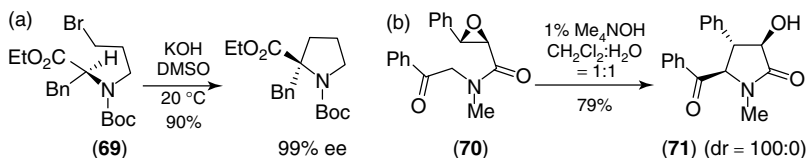
### 2.1.2.2 Cyclization via C<sub>2</sub>–C<sub>3</sub> Bond Formation

Several methods for the construction of pyrrolidine ring by forming the C<sub>2</sub>–C<sub>3</sub> bond have been reported. The highly enantioselective S<sub>N</sub>i cyclization reactions reported independently by Kawabata [56] and Kolaczowski [57] (**69**, Scheme 2.26a) involve the extension of the concept of memory of chirality developed by Fuji and coworkers.

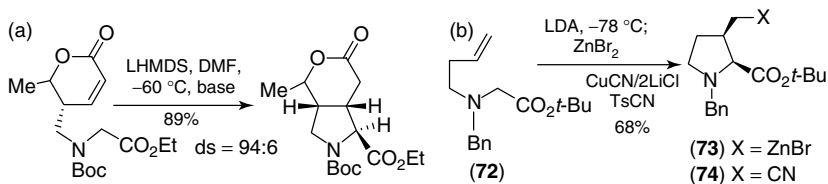
In Tian's asymmetric synthesis of dehydroclausenamide, a highly diastereoselective nucleophilic epoxide-opening reaction was used as the key step. When using a 1:1 CH<sub>2</sub>Cl<sub>2</sub>:H<sub>2</sub>O mixture as the biphasic solvent, the reaction of **70** provided the lactam **71** as a single product (Scheme 2.26b) [58].

In Fukuyama's synthesis of (–)- $\alpha$ -kainic acid, a highly stereoselective intramolecular Michael addition reaction was used as the key step (Scheme 2.27a) [59].

The amino-zinc-ene-enolate cyclization developed by Karoyan and coworkers [60] turned out to be a stereoselective method for the synthesis of *cis*-3-substituted proline. The zinc intermediate **73** formed during the reaction can be further



**Scheme 2.26** Synthesis of pyrrolidines by S<sub>N</sub>i reactions.



**Scheme 2.27** Synthesis of pyrrolidines by intramolecular Michael addition and the amino-zinc-ene-enolate cyclization.

functionalized. For example, tandem cyclization–cyanation of **72** gave **74** in good overall yield (Scheme 2.27b) [60].

Recently, Szymoniak reported a novel method for the construction of the pyrrolidine ring via a tandem hydrozirconation–stereoselective Lewis acid–mediated cyclization [61]. By using *N*-3-alkenylcarbamates as the starting material and replacing Lewis acid by *n*-butyllithium the above-mentioned concept was applied to the asymmetric synthesis of pyrrolidin-2-ones (Scheme 2.28).

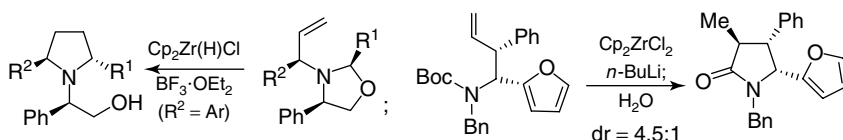
### 2.1.2.3 Cyclization Involving C<sub>3</sub>–C<sub>4</sub> Bond Formation

Dieckmann reaction of the chiral  $\beta$ -amino ester, prepared by Davies' asymmetric aza-Michael addition method, was shown to give good regioselectivity through the  $\beta$ -aminoenolate. The use of Weinreb amide served as a better electrophilic component. Similarly, intramolecular Thorpe reaction of a chiral dicyanide also gave good regioselectivity (Scheme 2.29a) [62].

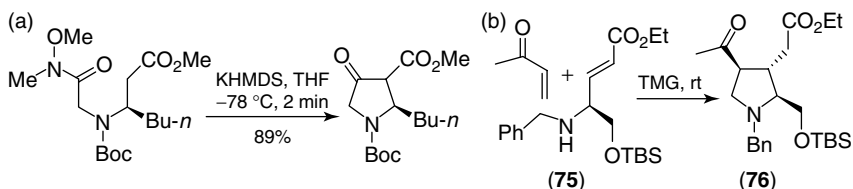
In a synthesis of kainoic acid, the reaction of methylvinyl ketone (MVK) with the Michael donor–acceptor  $\alpha$ -amino- $\alpha,\beta$ -unsaturated ester **75** proceeded smoothly to give the tandem Michael addition product **76** in 90% yield (Scheme 2.29b) [63].

In the synthesis of salinosporamide A (**4**), an even more effective proteasome inhibitor than omuralide, Corey and coworkers developed two highly diastereoselective syntheses of the highly substituted lactam intermediates via an internal Kulinkovich reaction (Scheme 2.30a) [64], and an internal Baylis–Hilman–aldol reaction (Scheme 2.30b) [65].

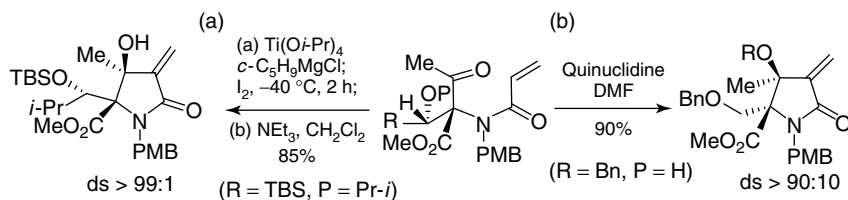
In the synthesis of the amino acid moiety of polyoxypeptins A/B, the SmI<sub>2</sub>-mediated Barbier-type cyclization of iodoketone **77** led to the desired diastereomer in 97:3 (Scheme 2.31a) [66].



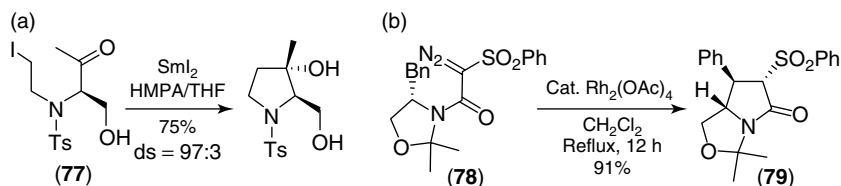
**Scheme 2.28** Synthesis of pyrrolidines/pyrrolidin-2-ones by tandem hydrozirconation–cyclization.



**Scheme 2.29** Synthesis of pyrrolidine derivatives by Dieckmann reaction and tandem Michael addition (KHMDS = potassium hexamethyldisilylamide).



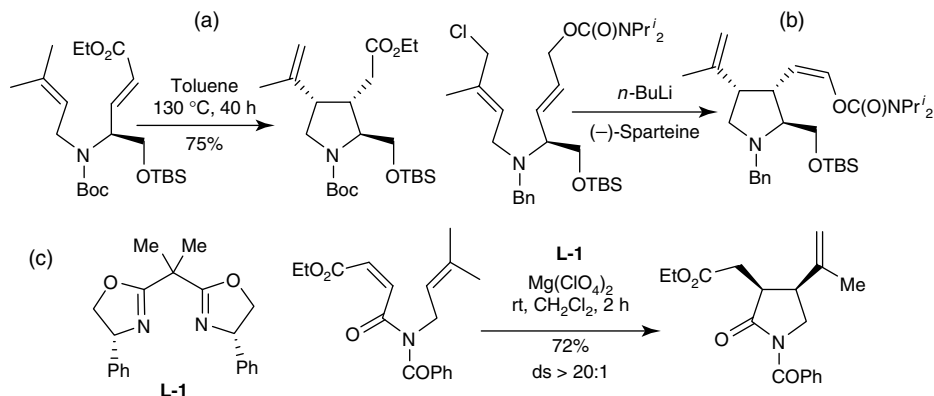
**Scheme 2.30** Corey's approaches to the intermediates for the synthesis of salinosporamide A.



**Scheme 2.31** Synthesis of pyrrolidine/pyrrolidin-2-one by radical cyclization and carbene insertion.

Rh-Catalyzed intramolecular carbene C–H insertion of diazo compound **78**, derived from  $\alpha$ -amino acid in six steps, gave the chiral  $\gamma$ -lactam **79** with high regio- and diastereoselectivity (Scheme 2.31b) [67].

In association with the synthesis of kainoids, several useful methods have been developed for the construction of pyrrolidine ring by  $\text{C}_3\text{--C}_4$  bond formation. They include, among others, Oppolzer's intramolecular thermal type I Ene reaction (Scheme 2.32a) [68], Hoppe's (–)-sparteine-mediated asymmetric deprotonation–cycloalkylation (Scheme 2.33b) [69], and Ganem's catalytic enantioselective metallo-ene reaction (Scheme 2.32c) [70].



**Scheme 2.32** Three typical approaches to kainoic acid skeleton.



## 2.1.3

## Cycloaddition Methods

## 2.1.3.1 Cycloaddition Approach

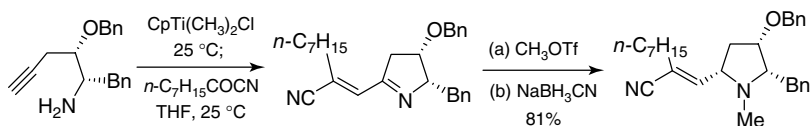
Imidotitanium-alkyne  $[2 + 2]$  cycloaddition of aminoalkynes provides an approach to cyclic imines, as used in the asymmetric synthesis of (+)-preussin (**15**) (Scheme 2.33) [71].

An interesting highly diastereoselective approach to C2/C3 *trans*-pyrrolidines was developed by Lautens, consisting of a magnesium iodide-mediated ring expansion of methylenecyclopropane **80** in the presence of a chiral sulfimine (Scheme 2.34a) [72]. This reaction was applied to a total synthesis of (–)- $\alpha$ -kainic acid (**2**).

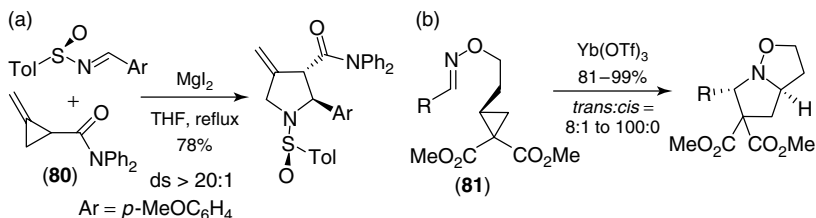
Kerr and coworkers reported another one-step synthesis of polysubstituted pyrrolidines by Yb(OTf)<sub>3</sub>-catalyzed reaction of oxime ethers with cyclopropane diesters in an inter- or intramolecular manner. By using the oxime ether-tethered cyclopropane diesters, the highly stereospecific annulation reaction was extended to a wider range of substrates (**81**, Scheme 2.34b) [73]. The reaction of *Z*-oxime ethers produce 2,5-*trans*-pyrrolo-isoxazolidines, whereas *E*-oxime ethers lead to 2,5-*cis* adducts. Starting with *N*-unsubstituted oxime ethers, *cis* adducts can be obtained in high diastereoselectivity via a three-component reaction.

1,3-Dipolar cycloaddition of azomethine ylides with electron-deficient alkenes (dipolarophile) constitutes a direct approach to 3,4-disubstituted pyrrolidines (Scheme 2.35) [74]. Several molecular motifs can be used to generate the dipoles. For example, aziridines (**82**) is a class of synthetic equivalents of azomethine ylides, which upon thermolysis, undergo a ring-opening reaction to produce the corresponding *N*-substituted azomethine ylides (**83**) [75].

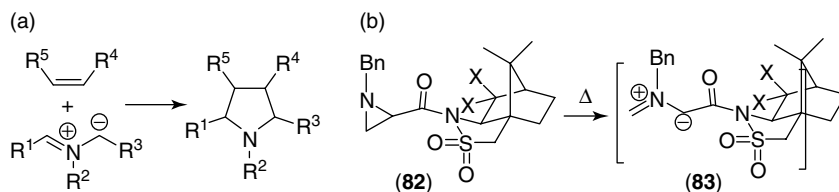
Azomethine ylides, generated *in situ* from imino esters, are another class of chiral 1,3-dipoles that can react with electron-deficient alkenes with good diastereomeric control (Scheme 2.36). In Scheme 2.36, a large-scale catalytic asymmetric



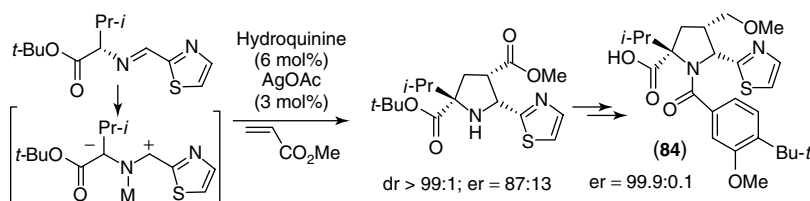
**Scheme 2.33** Imidotitanium-alkyne  $[2 + 2]$  cycloaddition approach to (+)-preussin.



**Scheme 2.34** MgI<sub>2</sub>-mediated ring expansion of methylenecyclopropane and annulation of oxime ethers with cyclopropane diesters.



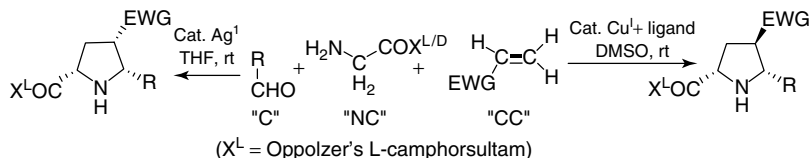
**Scheme 2.35** 1,3-Dipolar cycloaddition approach to pyrrolidines and the generation of an azomethine ylide from a chiral aziridine.



**Scheme 2.36** 1,3-Dipolar cycloaddition of the  $\alpha$ -amino azomethine ylides generated from  $\alpha$ -amino imines.

[3 + 2] cycloaddition of methyl acrylate and the *N*-metalated azomethine ylide for an asymmetric synthesis of an inhibitor of HCV polymerase (84) are outlined [76]. The alkaloid plays the roles of both a chiral ligand and as a base for the formation of the azomethine ylide or 1,3-dipole.

Starting from the chiral auxiliary-induced asymmetric [3 + 2] cycloaddition, Garner and coworkers developed an imaginative [C+NC+CC] reaction, which provides a highly efficient and flexible approach to highly functionalized pyrrolidines in a single operation and under mild conditions. In this context,  $\text{Ag}^+$ -catalyzed asymmetric three-component reaction using Oppolzer's L-camphor sultam as a chiral auxiliary provides a reliable means to control the *endo*-selective [3 + 2] cycloaddition, leading to 4,5-*cis* disubstituted pyrrolidines (Scheme 2.37) [77], while  $\text{Cu}^{\text{I}}$ -catalyzed reaction allows an access to 4,5-*trans* disubstituted pyrrolidines [78]. The methods involve a cascade imine formation, azomethine ylide formation, and 1,3-dipolar cycloaddition sequence.



**Scheme 2.37** Garner's stereocomplementary asymmetric "2 + 2 + 1" approaches to proline derivatives.

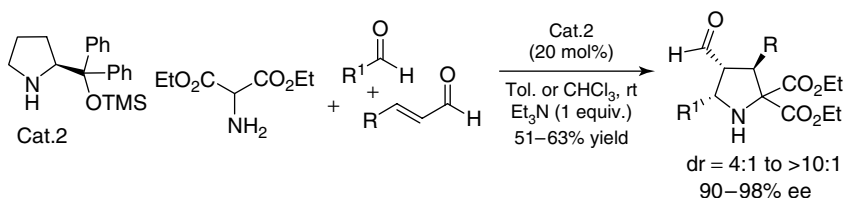
Recently, this concept was extended to an organocatalytic version. The protected diphenylprolinol-catalyzed, enantioselective, three-component coupling between aldehydes, dialkyl 2-aminomalonates, and  $\alpha,\beta$ -unsaturated aldehydes gives access to highly substituted pyrrolidines in good yield with >10:1 diastereoselectivity and 90–98% ee (Scheme 2.38) [79].

### 2.1.3.2 Annulation Approach

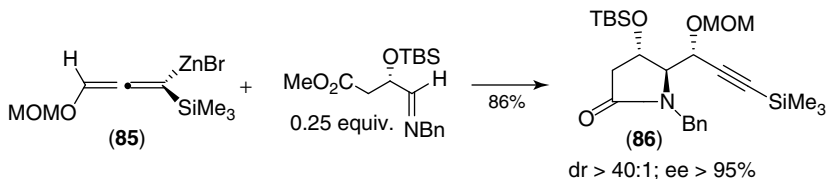
Pyrrolidines and pyrrolidine-2-ones can be synthesized by nucleophilic ring opening of optically active aziridines in a [3 + 2] annulation manner [80]. Reaction of configurationally stable alkoxy allenylzinc reagent **85** with the imine derived from (*S*)-malic acid furnished a route to pyrrolidin-2-one **86** with *anti-anti* stereochemistry (Scheme 2.39) [81].

A novel [4 + 1] annulation method for the efficient synthesis of diastereomerically and enantiomerically pure 2,3-disubstituted pyrrolidines is shown in Scheme 2.40. The method involves a sulfoxonium ylide-based aza-Payne rearrangement of the 2,3-aziridin-1-ols and the subsequent [1 + 4] annulation reaction [82].

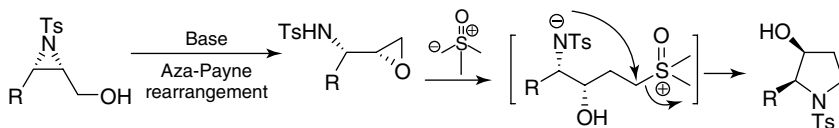
Lewis acid-catalyzed [3 + 2] annulation [83] of optically active *N*-Ts- $\alpha$ -amino aldehydes and 1,3-bis(silyl)propenes opens another one-step access to polysubstituted pyrrolidines in excellent diastereoselectivity (98:2). The conversion of the silyl group into a hydroxyl group by Tamao oxidation allows the total synthesis of polyhydroxylated alkaloids (Scheme 2.41) [84].



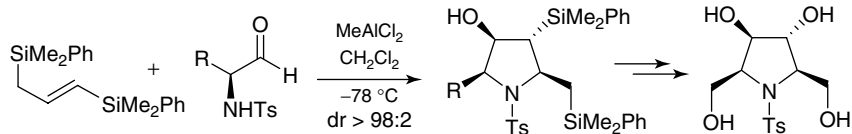
**Scheme 2.38** Organocatalytic, three-component synthesis of highly substituted pyrrolidines.



**Scheme 2.39** Normant's [3 + 2]-annulation approach to substituted pyrrolidin-2-ones.



**Scheme 2.40** Borhan's [4 + 1] annulation approach to 2,3-disubstituted pyrrolidines.



**Scheme 2.41** Synthesis of substituted pyrrolidines via a Lewis acid-catalyzed [3 + 2] annulation.

#### 2.1.4

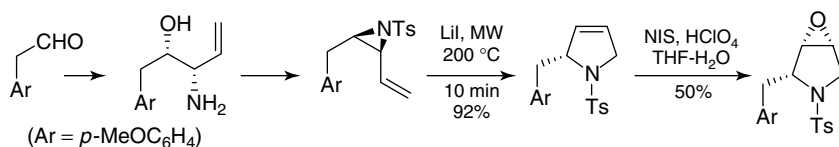
#### Ring Transformation Methods

##### 2.1.4.1 Ring Expansion Methods

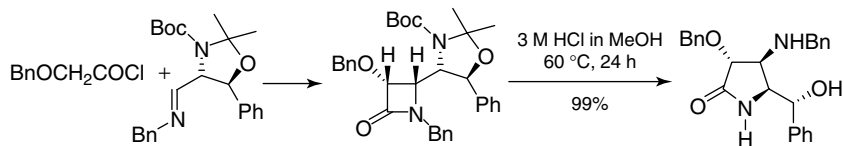
In a formal synthesis of (–)-anisomycin (**1**), Somfai *et al.* showed that microwave-assisted rearrangement of vinylaziridines provides an easy access to 3-pyrrolines (Scheme 2.42) [85].

The  $\beta$ -lactam skeleton has been recognized as a valuable precursor for the synthesis of pyrrolidine-2-ones via ring expansion [86]. For example, upon treatment of *N*-unsubstituted 4-( $\alpha$ -aminoalkyl)  $\beta$ -lactam with methanolic HCl at 60 °C for 2–24 h, the expected rearrangement occurred smoothly to give the pyrrolidine-2-one bearing four contiguous chiral centers in almost quantitative yield. The starting  $\beta$ -lactams are easily available via the Staudinger reaction (Scheme 2.43) [87].

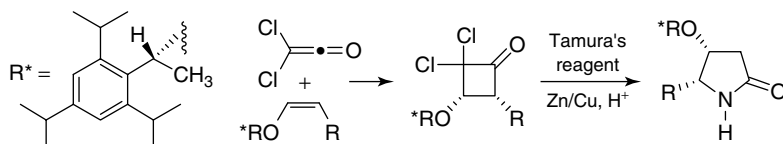
Using Tamura's Beckmann reagent, *O*-(mesitylenesulfonyl) hydroxylamine (MSH), Greene *et al.* developed a chiral auxiliary-induced, regio-controlled cyclobutanone  $\rightarrow$  pyrrolidinone ring expansion reaction. This, after dechlorination with zinc–copper coupling, led to *cis*-pyrrolidin-2-ones in high yields (Scheme 2.44). Using this strategy, they accomplished the total syntheses of pyrrolidine alkaloids (+)-preussin (**15**) [88a], (–)-anisomycin (**1**) [88b], and (–)-detoxinine [88c].



**Scheme 2.42** Microwave-assisted rearrangement of vinylaziridines to 3-pyrrolines *en route* to (–)-anisomycin.



**Scheme 2.43** Ring expansion of  $\beta$ -lactam derivatives to pyrrolidine-2-one derivative.



**Scheme 2.44** Greene's synthesis of *cis*-4,5-disubstituted pyrrolidin-2-ones by cyclobutanone ring expansion.

#### 2.1.4.2 Ring Contraction Methods

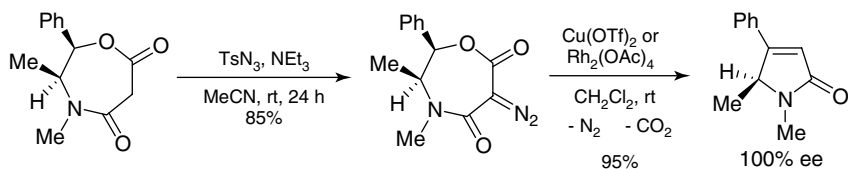
Although rarely used in pyrrolidine syntheses, the carbene ring contraction–decarboxylation of (2*R*,3*S*)- and (2*S*,3*R*)-6-diazo-3,4-dimethyl-2-phenyloxazepane-5,7-diones opens an easy regiospecific entrance to (*S*)- and (*R*)-1,5-dimethyl-1-4-phenyl-1,5-dihydro-2*H*-pyrrol-2-ones in enantiomeric pure forms (Scheme 2.45) [89].

Chiral auxiliary-induced, diastereoselective hetero-Diels-Alder reaction of nitroso derivatives and the subsequent reductive ring contraction of the resulting 1,2-oxazines under catalytic hydrogenolytic conditions constitutes a useful approach to dihydroxypyrrolidines (Scheme 2.46) [90].

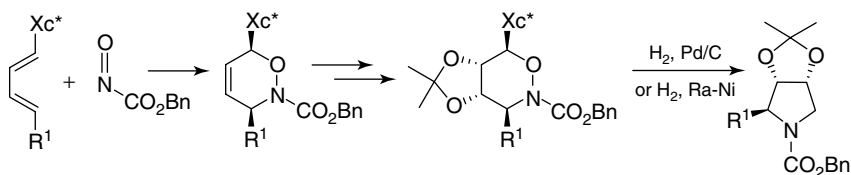
#### 2.1.5

##### Substitution of Already Formed Heterocycle

A number of approaches are available for the functionalization of a pyrrolidine/pyrrolidin-2-one ring at C-2 because of its presence in many alkaloids, including pyrrolidines, pyrrolizidines, and indolizidines alkaloids. Hence, the synthesis of 2-alkyl and 2,5-dialkyl pyrrolidines has attracted much attention [91].



**Scheme 2.45** Regiospecific ring contraction of oxazepane-5,7-dione to  $\alpha,\beta$ -unsaturated pyrrolidin-2-one derivatives.

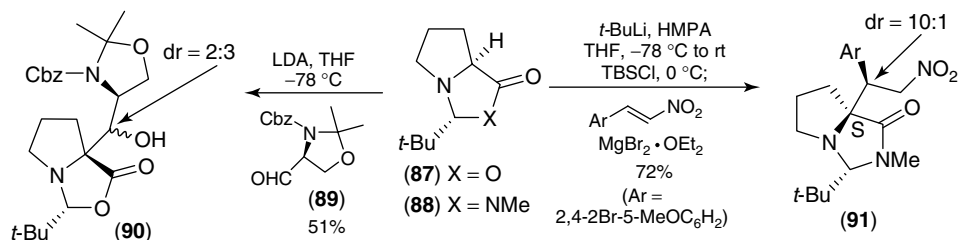


**Scheme 2.46** Stereoselective access to dihydroxylated pyrrolidines by reductive ring contraction of 1,2-oxazines.

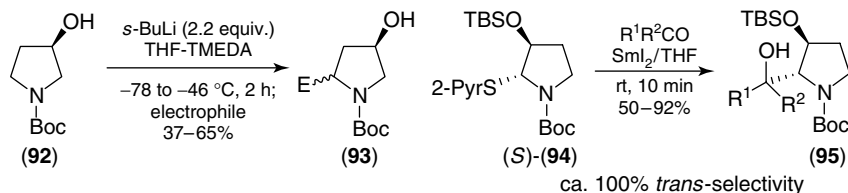
With Seebach's SRS methodology (self-regeneration of stereochemistry), single-enantiomer proline and pyroglutamate may serve as reliable chiralons for the generation and reaction of pyrrolidine  $\alpha$ -carbanions [92]. It was shown that the alkylation of the enolate proceeds *cis* with respect to the *tert*-butyl group ("cis rule"), with overall retention of configuration. For example, in the first total synthesis of kaitocephalin, the condensation of **87** with **89** led only to *cis* adducts **90** (Scheme 2.47) [93]. In contrast, the  $\text{MgBr}_2 \cdot \text{OEt}_2$ -mediated conjugate addition of the silyl enol ether, formed *in situ* from the *N,N*-acetal **88**, with a nitroolefin resulted in a 10:1 mixture of two *trans* diastereomers **91**. The major diastereomer **91** was used as a key intermediate for the synthesis of the marine alkaloid (–)-amathaspiramide F [94].

*tert*-Butoxycarbonyl (Boc) is an efficient group for the stabilization of  $\alpha$ -amino carbanions. The deprotonation of *N*-Boc-pyrrolidin-3-ol **92** occurred regioselectively at C-5. The reaction of the resulting dianion with electrophiles yielded a 1:1 diastereomeric mixture in each case tested except with methyl iodide (*dr* = 5:1) (Scheme 2.48) [95, 96]. The  $\text{SmI}_2$ -mediated reaction of the *N,O*-diprotected 2-pyridyl 3-pyrrolidinol-2-yl sulfide **94** with carbonyl compounds affords the protected *N*- $\alpha$ -hydroxyalkyl-3-pyrrolidines **95** with excellent diastereoselectivity at the newly formed chiral center in the pyrrolidine ring [97].

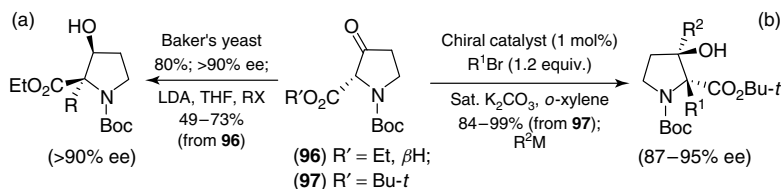
Asymmetric alkylation of the  $\beta$ -hydroxyproline ethyl ester *N*-carbamate, prepared by enantioselective reduction of **96** with Baker's yeast, was shown to proceed with net retention of configuration. By developing this method, Williams *et al.* achieved a total asymmetric synthesis of paraherquamide A (Scheme 2.49a) [98].



**Scheme 2.47** Syntheses of proline derivatives with Seebach's SRS methodology. HMPA = hexamethylphosphoramide and TBSCl = *tert*-butyldimethylsilyl chloride.



**Scheme 2.48** Synthesis of 5- or 3-substituted pyrrolidin-3-ols via the pyrrolidine C-2 carbanion intermediates. TMEDA = *N,N,N',N'*-tetramethyl-1,2-diaminoethane.

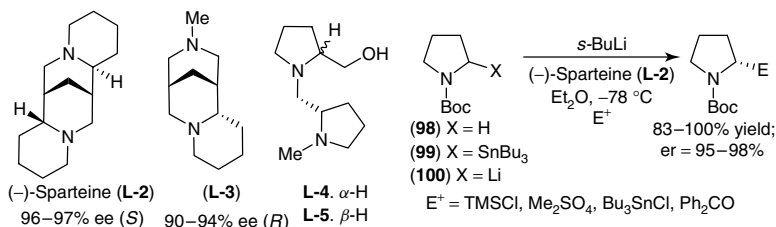


**Scheme 2.49** Syntheses of substituted 3-hydroxyproline derivatives by alkylation.

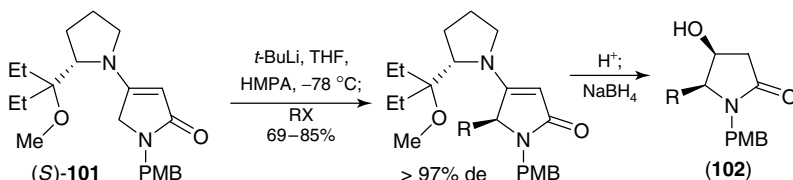
A phase-transfer-catalyzed alkylation strategy developed by Maruoka provides an efficient and high-yielding approach to another diastereomer and its derivatives (Scheme 2.49b) [99].

Beak and coworkers showed that enantioselective deprotonation (lithiation) of *N*-Boc-pyrrolidine (**98**) can be achieved using *sec*-BuLi/(–)-sparteine (**L-2**). The carbanion thus generated (**100**,  $\alpha$ -Li) reacts with electrophiles to give 2-substituted pyrrolidines with high enantioselectivities (Scheme 2.50) [95, 100]. The unnatural ligand **L-3** developed by O'Brien allows access to another enantiomer of the 2-substituted pyrrolidines [101]. Coldham's ligands **L-4**/**L-5** afford a highly enantioselective dynamic kinetic resolution pathway of the racemic organolithium **100**, derived from **98** or **99** by deprotonation or by tin–lithium exchange [102]. Gawley showed that the tin–lithium exchange of enantioenriched 2-stannylpyrrolidine **99** affords configurationally stable 2-lithiopyrrolidine **100** with retention of configuration [103].

Through the reaction sequence displayed in Scheme 2.51, tetramate derivative **101** turned out to be a valuable synthetic equivalent of the 4-hydroxypyrrolidin-2-one 2-carbanion synthon, which is used for the synthesis of pyrrolidin-2-ones **102** [104].



**Scheme 2.50** Methods for the generation and reaction of configurationally stable enantioenriched *N*-Boc 2-lithiopyrrolidine.



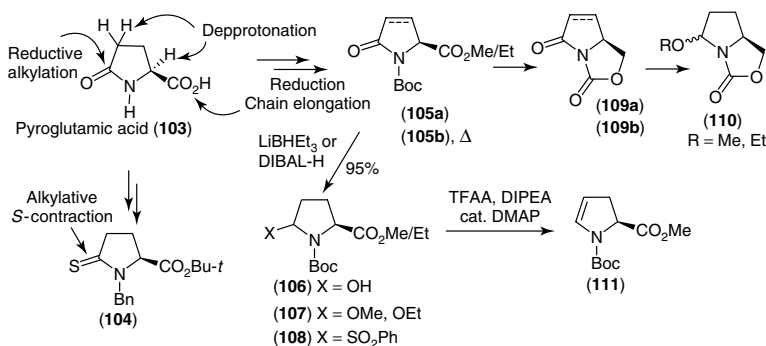
**Scheme 2.51** A flexible approach to *cis*-5-alkyl-4-hydroxypyrrolidin-2-ones.

### 2.1.5.1 By Nucleophilic Reaction of Pyrrolidinium Ions

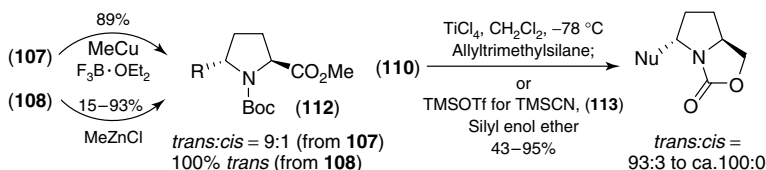
Because of its double functionality and easy availability, (*S*)-pyroglutamic acid is a versatile useful chiron (Scheme 2.52) [105] for the asymmetric synthesis of 2,5-disubstituted pyrrolidines [106], pyrrolizidines [107], and indolizidines [108].

Both the lactam carbonyl and carboxyl groups in pyroglutamic acid can be employed to introduce side chains. Elongation of the carboxyl group can be achieved by reduction to a hydroxymethyl group followed by tosylation and coupling with an organocopper reagent [106, 107], or by transformation into a formyl group, followed by Kocienski's modification of Julia olefin synthesis [108]. The amide carbonyl can be used to install a second alkyl group via the corresponding thiolactam by Eschenmoser sulfide contraction reaction [109], via enamino diester derivative [106, 107], or via thioimide derivative [106].

A more versatile method for the activation of lactams consists in converting lactams into the corresponding *N*-carbamates (imides). After their regioselective partial reduction with diisobutyl aluminium hydride (DIBAL-H) or Super hydride, they are converted into *N,O*-acetals and subjected to Lewis acid-promoted  $\alpha$ -amidoalkylation with lower order organocuprates (**107**  $\rightarrow$  **112**, Scheme 2.53) [110] or with Si-nucleophiles (**110**  $\rightarrow$  **113**) [111]. The latter reaction can also be achieved by Ley's sulfone chemistry [112] (**108**  $\rightarrow$  **112**) [113]. Martin's improvements over the stepwise reductive alkylation method [114] provides a general and highly chemo- and diastereoselective reductive alkylation (**114**  $\rightarrow$  **115**, Scheme 2.54) [115]. It is well recognized that the  $\alpha$ -aminoalkylation passes through *N*-acyliminium ion intermediates [116].

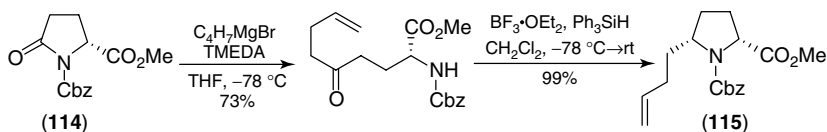


**Scheme 2.52** Conversion of pyroglutamic acid into useful synthetic intermediates.

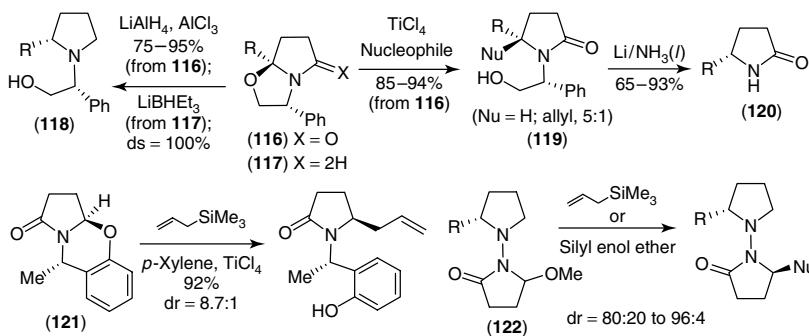


**Scheme 2.53** Summary of the stereoselective  $\alpha$ -amidoalkylation of the *N,O*-acetals derived from (*S*)-pyroglutamic acid.





**Scheme 2.54** Martin's modified reductive alkylation method.



**Scheme 2.55** The  $\alpha$ -amidoalkylation reactions of Meyers' and Kibayashi's chiral *N,O*-acetals.

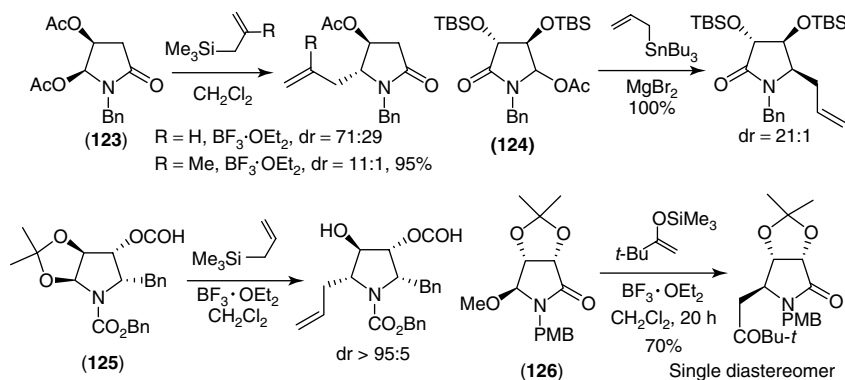
A simple asymmetric synthesis of 2-substituted pyrrolidines (**116**  $\rightarrow$  **118**, Scheme 2.55) [117] and 5-substituted pyrrolidin-2-ones (**116**  $\rightarrow$  **119**) [118] starting from  $\gamma$ -keto acid and (*R*)-phenylglycinol was developed by Meyers *et al.* [119]. This method was extended to the (*R*)-phenylglycinol-derived bicyclic 1,3-oxazolidine **117** [120]. The *N,O*-acetals bearing easily cleavable chiral auxiliaries **121** [117] and **122** [121] were developed by Kibayashi *et al.* and were shown to give good stereoselectivities in the  $\alpha$ -amidoalkylation. Except one case [122], retention of configuration was observed in the above-mentioned reactions.

The  $\alpha$ -amidoalkylation of *N,O*-acetals **123** [123], **125** [124] and **126** [125] with trimethylallylsilane and silyl enol ether give the corresponding products with excellent *trans* diastereoselection (Scheme 2.56). By contrast, the reactions of *O*-TBS-protected *N,O*-acetals derived from tartaric acid (**124**) [126], malic acid [127], and related compounds [128] were shown to give good-to-excellent *cis* diastereoselectivities.

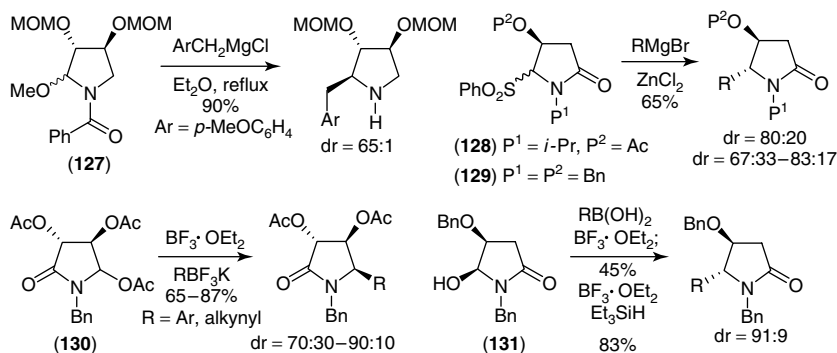
The  $\alpha$ -amidoalkylation of *N,O*-acetals **127** [129], **128** [130], and **129** [131] and also the borono-Mannich reaction of **131** [132] with more flexible carbon nucleophiles are *trans*-diastereoselective (Scheme 2.57). By contrast, reactions of *O*-acetyl-protected *N,O*-acetals derived from tartaric acid (**130**) [133] give *cis* diastereomers as major products.

### 2.1.5.2 By Nucleophilic Reaction of Cyclic Imides

Results from Yoda's laboratory [134] show that the reductive alkylation of the  $C_2$ -symmetrical tartarimides is a better alternative to the  $\alpha$ -amidoalkylation reaction displayed in Schemes 2.56 and 2.57 both in terms of chemical yields and in *trans*-diastereoselectivities (Scheme 2.58a) [134a]. They applied this method to the



**Scheme 2.56**  $\alpha$ -Amidoalkylation reactions of the chiral pool-derived *N,O*-acetals.

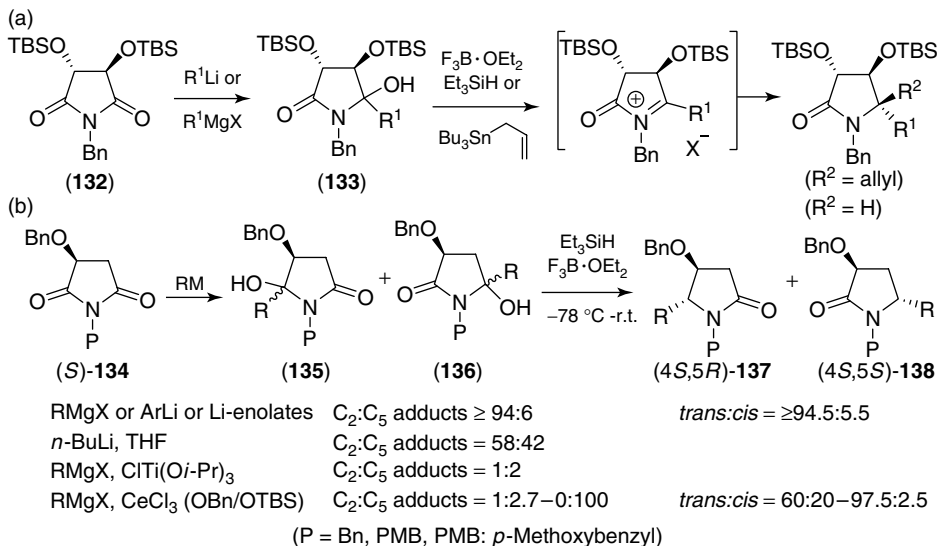


**Scheme 2.57**  $\alpha$ -Amidoalkylation reactions of chiral pool-derived *N,O*-acetals with organometallic compounds.

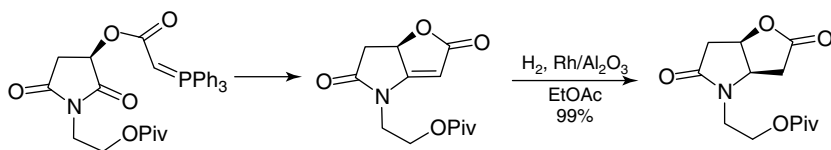
asymmetric synthesis of the pyrrolidine alkaloid codonopsinine (**22**) [134b]. Pilli *et al.* showed that the Grignard addition products, *N,O*-acetals **133**, can undergo an  $\alpha$ -amidoalkylation with allyltributyltin leading to the formation of a quaternary stereocenter [135a].

Regioselectivity in the reductive alkylation of the protected malimides [136] was shown to be dependent on the protecting group [136b]. Moreover, the reaction of the *O*-benzyl-protected malimides with Grignard reagents gives excellent C-2 regioselectivity [136], while addition of organocerium reagents affords C-5 adducts as the major products (Scheme 2.58b) [135b]. In both cases, subsequent reductive dehydroxylation reactions give excellent *trans* diastereoselectivities. Unexpectedly, the reaction of malimides with organotitanium reagents gives only modest regioselectivity [137].

The intramolecular Wittig reaction of a malimide derivative followed by stereoselective hydrogenation was used as key steps in a highly regio- and diastereoselective synthesis of the Geissman–Waiss lactone (Scheme 2.59) [138].



**Scheme 2.58** The stepwise reductive alkylation of tartarimides and malimides.

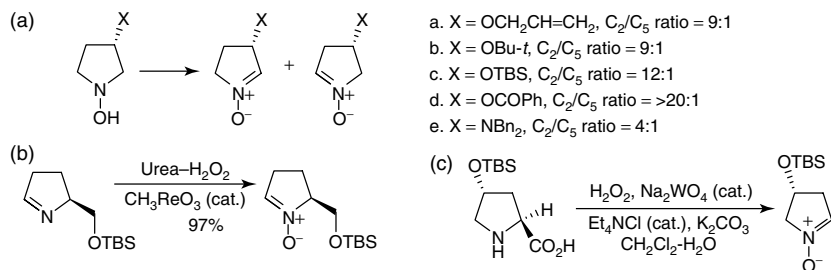


**Scheme 2.59** A highly regio- and diastereoselective synthesis of the Geissman–Waiss lactone.

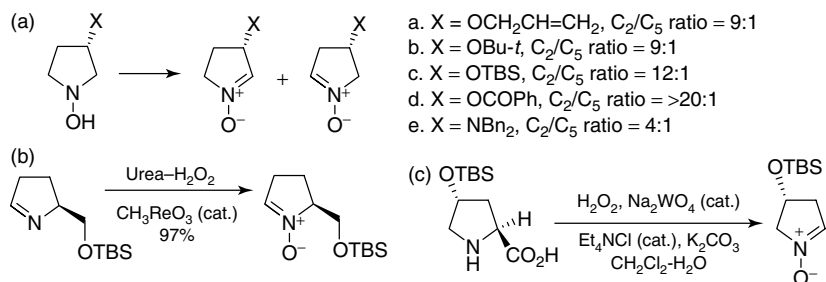
### 2.1.5.3 By Nucleophilic Addition/Cycloaddition of Pyrrolidine Nitrones

Enantioenriched pyrrolidine nitrones [139] are versatile building blocks for the asymmetric synthesis of pyrrolidines, pyrrolizidines, and indolizidines through nucleophilic addition [140] and 1,3-dipolar cycloaddition [141]. Pyrrolidine nitrones can be prepared by intramolecular condensation of a hydroxylamine with a carbonyl group or by oxidation of cyclic hydroxyamines, amines, and imines available from chiral pools such as tartaric acid, malic acid, and sugars.

For the synthesis of nitrones from unsymmetric *N*-hydroxypyrrolidines, such as those derived from malic acid, regioselectivity may be a problem. Fortunately, oxidation with yellow HgO was reported to give good regioselectivities (Scheme 2.60a) [142]. The environmentally friendly oxidant, bleach, gives only modest regioselectivities [143]. Catalytic oxidation of preformed imines by methyl trioxorhenium/urea hydrogen peroxide (Scheme 2.60b) eliminates the problem of regioselectivity [144], which is also the case by decarboxylative oxidation of  $\alpha$ -amino acids (Scheme 2.60c) [145].



**Scheme 2.60** Regioselective synthesis of chiral, nonracemic, unsymmetric nitrones.

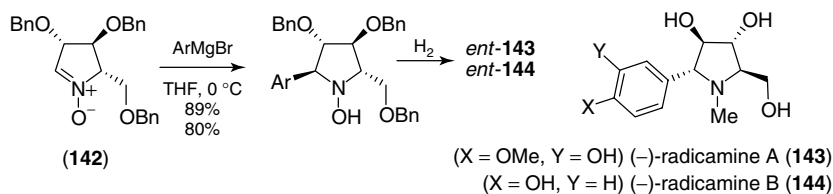


**Scheme 2.61** Stereoselective Grignard addition to nitrones.

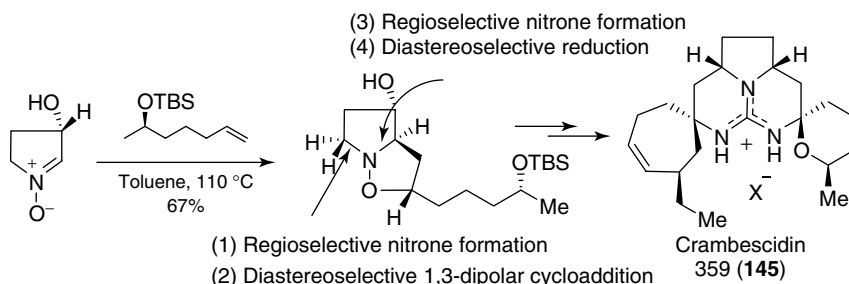
Stereoselection in Grignard additions to nitrones is substrate and reagent dependent. While the addition of benzylic Grignard reagents to nitrone **139** gave a 3:2 *trans/cis* selectivity, a 3:7 ratio was obtained by using magnesium bromide etherate as an additive (Scheme 2.61) [146]. The vinylation of nitrone **140** was shown to be entropy-controlled: a 93:7 *trans/cis* diastereomeric ratio was obtained independent of the reaction temperature [147]. Similarly, ZnI<sub>2</sub>-promoted reactions of ketene *t*-butyldimethylsilyl methyl/*t*-butyl acetals with nitrone **141** gave excellent *trans* diastereoselectivities [148].

The structural similarity between nitrone **142** and alkaloids radicamine A (**143**), radicamine B (**144**), as well as codonopsine and codonopsinine (**22**) justifies consideration of the former as the chiron for the synthesis of radicamines A and B. Indeed, starting from nitrone **142**, derived in seven steps from D-xylose, the antipodes of (+)-radicamine A and (+)-radicamine B were synthesized as the sole diastereomers respectively (Scheme 2.62) [149]. Similarly, (–)-codonopsine was synthesized from L-xylose [150].

Nitrones are excellent 1,3-dipoles for cycloaddition and, after cleavage of the N–O bond, can be used to introduce side chains at C-2 of pyrrolidine ring. The asymmetric total synthesis of marine natural product crambescidin 359 (**145**) nicely demonstrates the value of nitrone cycloaddition methodology for the asymmetric synthesis of pyrrolidines (Scheme 2.63) [151].



**Scheme 2.62** Asymmetric syntheses of radicamines A and B via nitron intermediates.

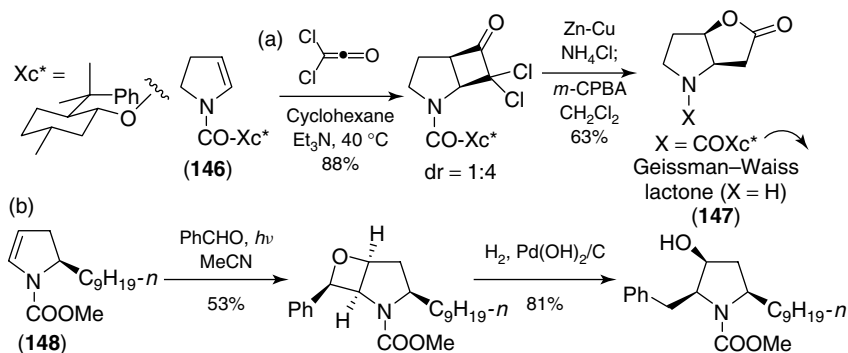


**Scheme 2.63** Asymmetric synthesis of crambescidin 359 via iterative selective nitron formation-1,3-dipolar cycloaddition.

#### 2.1.5.4 By Functionalization of 2-Pyrrolines

Three approaches are available for the functionalization of endocyclic enecarbamates (cf. Scheme 2.79). Ketene [2 + 2] cycloaddition with endocyclic enecarbamate 146, developed by Correia showed a 1:4 diastereoselectivity. An *meta*-chloroperoxybenzoic acid (CPBA)-mediated, regioselective Baeyer–Villiger oxidation led to the synthesis of the Geissman–Waiss lactone (147) (Scheme 2.64a) [152].

By applying the Paternò–Büchi reaction to the chiral 2-substituted 2-pyrroline 148 derived from pyroglutamic acid, Bach *et al.* developed a stereoselective



**Scheme 2.64** Synthesis of substituted pyrrolidines via [2 + 2] cycloaddition reactions of endocyclic enecarbamates.

*cis*-3-hydroxy-2-benylation of 2-pyrroline **148**. The key [2 + 2] photocycloaddition was shown to exhibit an unprecedented facial diastereoselectivity. Taking advantage of this reaction, a short total synthesis of (+)-preussin (**15**) was achieved (Scheme 2.64b) [153].

#### 2.1.5.5 By Enantioselective Reactions

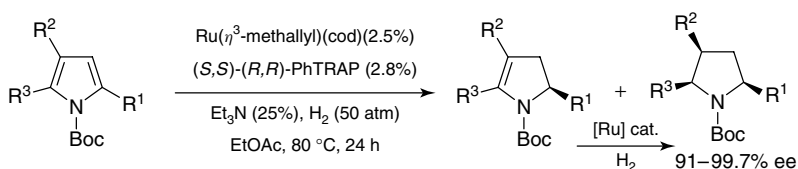
Catalytic hydrogenation of substituted pyrrole derivatives is a classical method for the synthesis of all-*cis*-substituted pyrrolidines. A catalytic enantioselective synthesis version of this method has recently been shown to give high enantioselectivities (Scheme 2.65) [154].

Direct asymmetric  $\alpha$ -substitution of pyrrolidine carbamates can be achieved by highly regio-, diastereo-, and enantioselective C–H insertion of methyl aryldiazoacetates. Using this method, both monosubstituted and C<sub>2</sub>-symmetric 2,5-*trans*-disubstituted pyrrolidines can be synthesized with high enantioselectivities (Scheme 2.66) [155a]. A Rh(II)–Carbenoid mediated, intramolecular C–H insertion reaction affords a short approach to both Geissman–Waiss lactone and the necine base (–)-turneforcidine [155b].

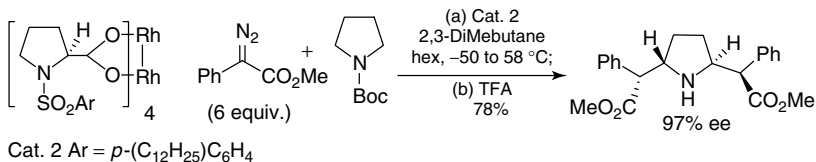
Katsuki found that asymmetric desymmetrization of *N*-*t*-butoxycarbonyl-*meso*-3,4-isopropylidenedioxy-pyrrolidine **149** can be effected through an enantiotropic selective oxidation using an (*R,R*)-(salen)manganese(III) complex as catalyst (Scheme 2.67) [156].

#### 2.1.5.6 By Functionalization at C<sub>3</sub>/C<sub>4</sub> Positions of Pyrrolidines

As shown in Scheme 2.52, pyroglutamic acid is not only suitable for the introduction of substituents at C<sub>2</sub> and C<sub>5</sub> positions but it has also been widely used to synthesize 3/4-substituted pyrrolidines/pyrrolidin-2-ones [105]. This can be done by deprotonation–substitution at  $\alpha$ -position of the lactam carbonyl group [157]. Through the formation of an  $\alpha,\beta$ -unsaturated lactam system (**105b** and **109b**, Scheme 2.52), a number of reactions can be realized in the olefin portion, including



**Scheme 2.65** Synthesis of all-*cis*-substituted pyrrolidines by catalytic enantioselective hydrogenation.

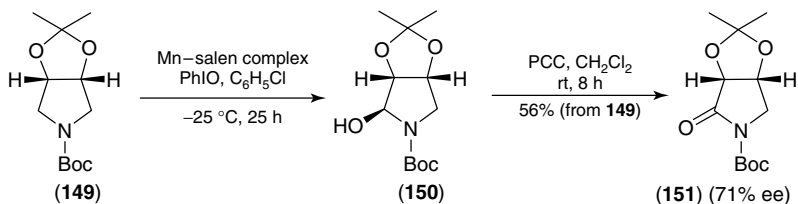


**Scheme 2.66**  $\alpha$ -Substitution of pyrrolidine carbamates by enantioselective C–H insertion.

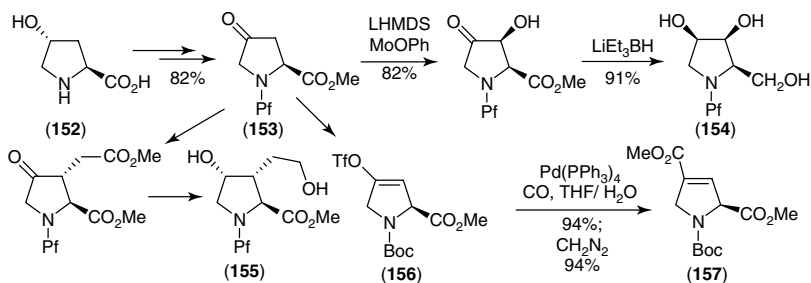
conjugate addition [158], tandem conjugate addition-trapping of enolate intermediates [159], epoxidation [160], and [2 + 3] dipolar cycloaddition reactions [160].

*Trans*-4-Hydroxyproline (**152**) constitutes another useful chiron for the synthesis of 3,4-dihydroxyprolinol derivatives. For example, it was converted into **153** [161], **154** [162], **155** [163], and **156** [164] (Scheme 2.68). Compounds **155** and **156** were used in a total synthesis of  $\alpha$ -kainic acid [162, 163].

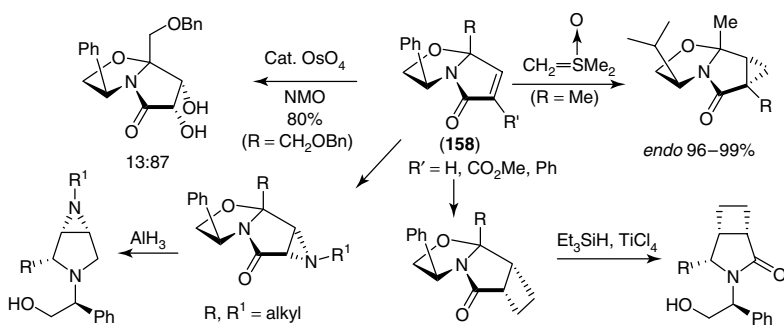
Meyers' chiral bicyclic lactams **158** are versatile building blocks for highly *endo*-selective  $\alpha$ -alkylations,  $\alpha,\alpha$ -dialkylations, cyclopropanations, and so forth (Scheme 2.69) [119].



**Scheme 2.67** Enantioselective  $\alpha$ -oxidation of pyrrolidine carbamates.



**Scheme 2.68** Some pyrrolidine derivatives derived from *trans*-4-hydroxyproline.



**Scheme 2.69** Selected transformations of the Meyers' chiral bicyclic lactams.

## 2.2 Pyrrolines

### 2.2.1

#### Synthesis of Pyrrolines by Cyclization and Annulation Reactions

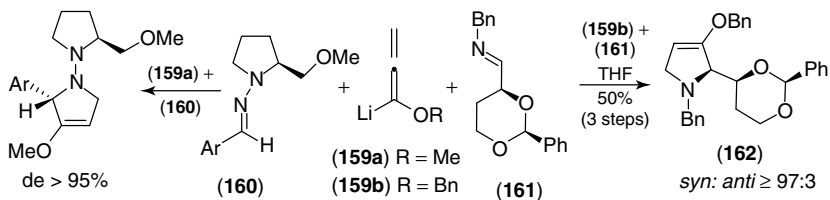
Several “2 + 3” annulation approaches to 2-pyrrolines have been reported. Goré [164] and Reißig [165] independently developed a one-pot “3 + 2” annulation approach to 2-pyrroline derivatives (Scheme 2.70). The chiral inducer may be a part of the molecule or introduced as a chiral auxiliary on either imines or alkoxyallenes. Using this method, a straightforward synthesis of (–)-detoxinine was achieved from the adduct **162** in five steps.

Recently, a catalytic enantioselective three-component synthesis of 4-arylated dehydropyrrolines was reported. In the presence of 10 mol% of  $[\text{Cu}(\text{MeCN})_4]\text{ClO}_4/(\text{R})\text{-Ti}(\text{BINAP})$  (cat. 3), the “3 + 2” annulation of allenylstannane with an  $\alpha$ -imino ester, followed by a tandem Stille coupling of the resulting 4-stannyl dehydropyrrolinate, gave 4-arylated dehydropyrrolines (Scheme 2.71) [166].

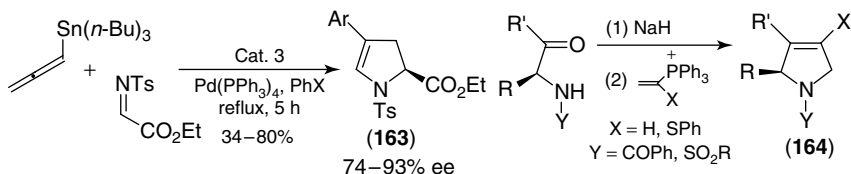
A tandem aza-Michael-type-reaction–Wittig reaction between  $\alpha$ -amide ketones and vinylphosphonium salts was reported to give 3-pyrrolines **164** and pyrrolizidines in high yields. The stereochemistry of the starting  $\alpha$ -amido ketone is retained during this process (Scheme 2.71) [167].

Nucleophilic addition of lithio propiolate to nitrones derived from D-glyceraldehyde and  $\alpha$ -amino aldehydes has been shown to give excellent diastereoselectivity. This opens a ready access to enantiopure 5-substituted-3-pyrrolin-2-ones [168]. After further refinement, Hanessian and coworkers applied this methodology to the total synthesis of A-315675 (**6**), a potent neuraminidase inhibitor (Scheme 2.72) [169].

Several ring-closing olefin metathesis (RCM) reaction based approaches to pyrrolines have been reported [170]. Sharpless asymmetric epoxidation [171],

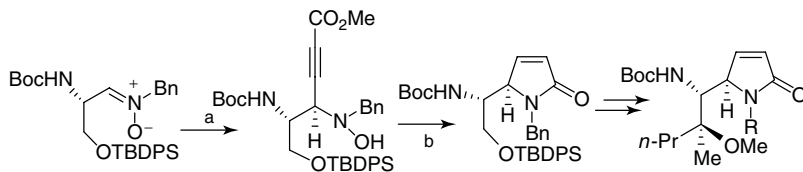


**Scheme 2.70** Goré’s and Reißig’s one-pot “3 + 2” annulation approaches to 3-pyrrolines.

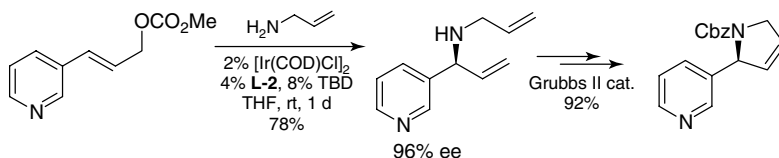


**Scheme 2.71** Two “3 + 2” annulation approaches to pyrrolines.





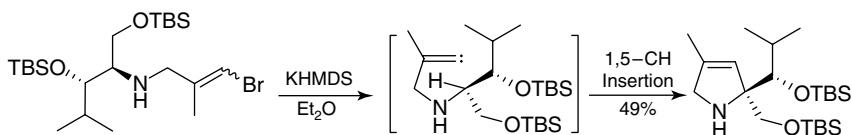
**Scheme 2.72** Hanessian's synthesis of 5-substituted-3-pyrrolin-2-ones.



**Scheme 2.73** Helmchen's enantioselective synthesis of (*R*)- and (*S*)-nicotine.

regioselective rhodium-catalyzed allylic amination [172], palladium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of vinyl epoxides [173], and Ir-catalyzed enantioselective allylic amination [174] (Scheme 2.73) have all been used to form the bis-allylic alicyclic precursors.

Hayes *et al.* developed a KHMDS-promoted stereospecific alkylidene carbene 1,5-CH insertion for the synthesis of substituted 3-pyrrolines (Scheme 2.74). This was used as a key step in an enantioselective total syntheses of omuralide, of its C<sub>7</sub>-epimer, and of (+)-lactacystin (**3**) [175].



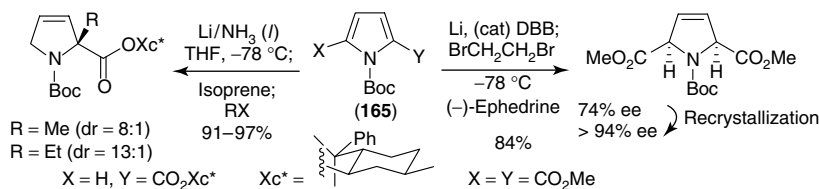
**Scheme 2.74** Synthesis of substituted 3-pyrrolines by base-promoted stereospecific alkylidene carbene 1,5-CH insertion.

### 2.2.2

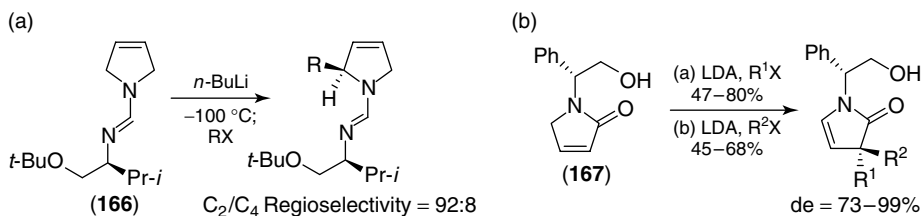
#### Synthesis of Pyrrolines by Substitution of Already Formed Heterocycles

Chiral auxiliary-induced, tandem Birch-type reduction–protonation/alkylation of *N*-Boc-pyrrole carboxylic ester/amide [176a,b] **165** gives rise to nonalkylated/alkylated 3,4-dehydropyrolines with good diastereoselectivities (Scheme 2.75) [176]. More interestingly, and through chiral protonation, enantioselective partial reduction of pyrrole 2,5-dicarboxylate can be achieved with good diastereo- and enantioselectivities following recrystallization [177].

Alkylation of a chiral, nonracemic formamidine developed by Meyers *et al.* affords a highly enantioselective entrance to 2-alkyl-3-pyrrolines (95–96% ee, Scheme 2.76a) [178], while Royer *et al.* showed that chiral nonracemic  $\alpha,\beta$ -



**Scheme 2.75** Donohoe's approaches to proline derivatives.



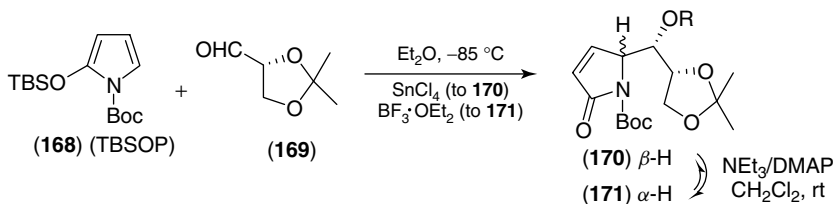
**Scheme 2.76** Diastereoselective approaches to 2-alkyl-3-pyrrolines and to  $\beta,\gamma$ -unsaturated lactams.

unsaturated  $\gamma$ -lactam **167** is a useful building block for the construction of  $\beta,\gamma$ -unsaturated lactams bearing a chiral quaternary center (Scheme 2.76b) [179].

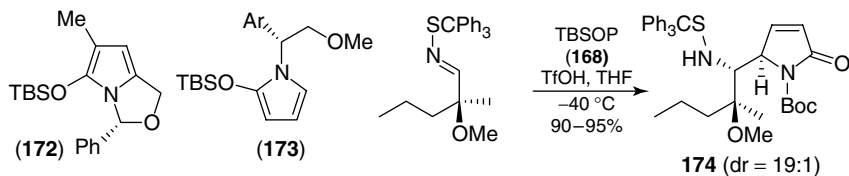
The vinylogous Mukaiyama-type aldol addition methodology, originally developed by Rassu/Casiraghi *et al.*, affords a versatile approach to chiral non-racemic  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams [180]. For example, in the presence of  $\text{SnCl}_4$ , the reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde (**169**) with *N*-(*tert*-butoxy carbonyl)-2-(*tert*-butyldimethylsiloxy) pyrrole (TBSOP) **168** gave D-arabino  $\alpha,\beta$ -unsaturated  $\gamma$ -lactam **170** as the sole product (Scheme 2.77) [180a]. However,  $\text{BF}_3$  etherate-mediated reaction led to D-ribo-epimer **171**. Moreover, a clean and almost quantitative epimerization at C-5 can be achieved by stirring lactam **170** with  $\text{Et}_3\text{N}$ /DMAP, which provides a good alternative preparation of the thermodynamically more stable D-ribo-lactam **171**.

The reactions of chiral 2-(*tert*-butyldimethylsiloxy) pyrroles **172** and **173** with achiral aldehydes were investigated independently by Baldwin and Royer and used in the syntheses of (+)-lactacystin (**3**) [181] and cephalotaxine [182] respectively.

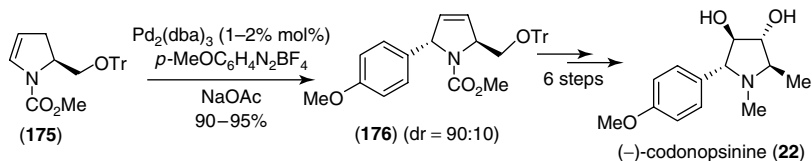
The Rassu/Casiraghi methodology is applicable to imines, which constitutes a vinylogous Mannich-type reaction [183]. The reaction of TBSOP (**168**) with chiral imines was used as a key step in the total synthesis of an influenza



**Scheme 2.77** Rassu/Casiraghi vinylogous Mukaiyama-type aldol addition methodology.



**Scheme 2.78** Two chiral 2-(*tert*-butyldimethylsiloxy) pyrroles and a vinylous Mannich-type reaction.



**Scheme 2.79** Correia's synthesis of (–)-codonopsinine.

neuraminidase inhibitor. It was found that the use of TfOH as a catalyst gave excellent diastereoselectivity and chemical yield (Scheme 2.78) [184].

Heck reaction of enecarbamates 175 derived from pyroglutamic acid with *p*-methoxybenzenediazonium tetrafluoroborate was shown to give 2,5-disubstituted 3-pyrroline 176 with good regio- and *trans*-diastereoselectivity. The product was converted into (–)-codonopsinine (22) in six steps (Scheme 2.79) [185].

## 2.3

### Fused Bicyclic Systems with Bridgehead Nitrogen

#### 2.3.1

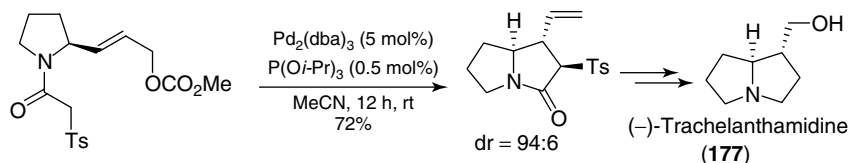
##### Pyrrolizidines

##### 2.3.1.1 Through Extension of Methods for the Synthesis of Pyrrolidines

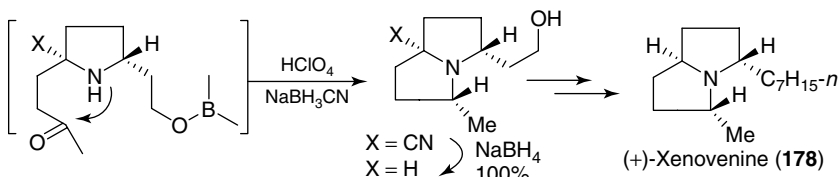
Because a pyrrolizidine can be viewed as a fused pyrrolidine, many methods developed for the asymmetric synthesis of pyrrolidines can be extended to pyrrolizidines [167,186–189]. Thus methods employed for the formation of pyrrolidine rings can be used to construct the pyrrolizidine ring system starting from pyrrolidine derivatives.

For example, the palladium-catalyzed cyclization of proline-derived allylic carbonates, initially developed for the synthesis of 4,5-*cis*-disubstituted  $\gamma$ -lactams, was extended to the synthesis of pyrrolizidinone, which led to a stereoselective synthesis of (–)-trachelanthamidie (177) (Scheme 2.80) [190].

Intramolecular reductive alkylation is a useful method widely used for the synthesis of pyrrolidines [116], and has also found widespread applications in the synthesis of pyrrolizidines and indolizidines. In the first enantioselective synthesis



**Scheme 2.80** Synthesis of pyrrolizidinones by palladium-catalyzed cyclization of proline-derived allylic carbonate.



**Scheme 2.81** Takano's intramolecular reductive alkylation approach to xenovenine.

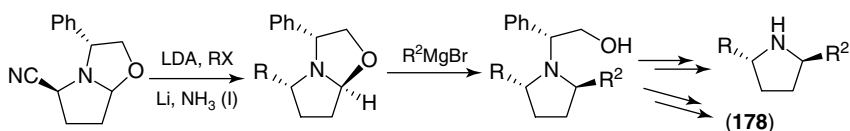
of the ant venom alkaloid xenovenine (**178**, Scheme 2.81) [191], double intramolecular reductive alkylation was employed to form the pyrrolizidine ring in high stereoselectivity. Later, this became a standard procedure for the synthesis of this alkaloid [192], as well as of other pyrrolizidine alkaloids such as the pyrrolizidines 239K', 265H', 267H' [193], epohelmin B [194a], as well as hyacinthacines A<sub>2</sub> and A<sub>3</sub> [194b].

Husson's synthesis of *trans*-2,5-dialkylpyrrolidines [192a] and xenovenine (**178**) [192b] is another demonstration of such an approach (Scheme 2.82) [192c]. Similarly, Greene's methodology [88] was extended to the synthesis of (+)-hyacinthacine A<sub>1</sub> [189a], (+)-amphorogynines A and D, and (+)-retronecine [189b].

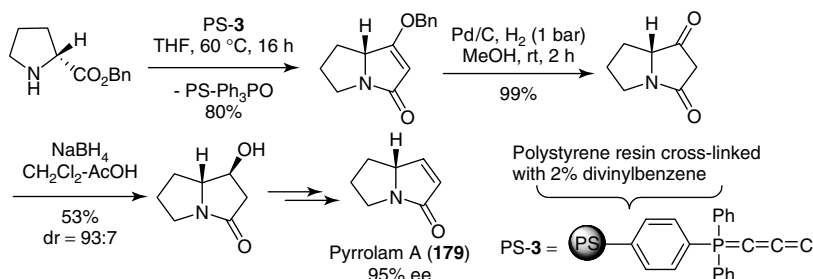
The cumulated ylide Ph<sub>3</sub>PCCO is a useful C<sub>2</sub><sup>a, d</sup> component. Its reaction with  $\alpha$ -amino esters can lead to tetramates [195a]. The reaction with (*R*)-prolinate gave, via a domino addition–Wittig reaction, bicyclic tetramate, which was converted into (–)-pyrrolam A (**179**) in four steps from prolinate (Scheme 2.83) [195b].

### 2.3.1.2 Other Methods for the Synthesis of Pyrrolizidines

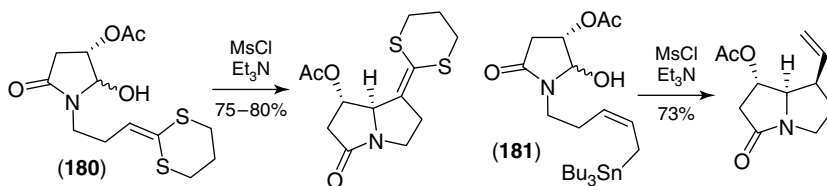
Formation of the pyrrolizidine ring system by intramolecular  $\alpha$ -amidoalkylation is a widely adopted strategy [116]. Ketene dithioacetal (**180**, Scheme 2.84) [196] and allyl tin (**181**) [197] were shown to be excellent nucleophiles for intramolecular  $\alpha$ -amidoalkylation. Using acetoxy-directed *N*-acyliminium ion-ketene dithioacetal cationic cyclization (of **180**) as the key step, Chamberlin *et al.* established a versatile



**Scheme 2.82** Husson's approach to pyrrolidines and pyrrolizidine.



**Scheme 2.83** Schobert's synthesis of (–)-pyrrolam A.



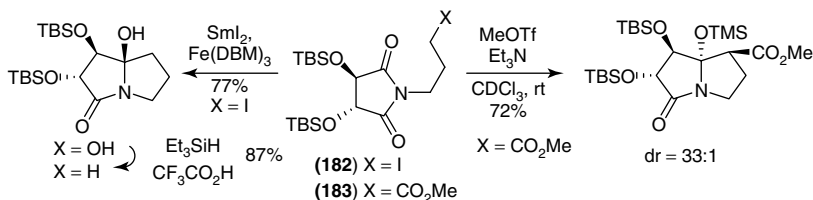
**Scheme 2.84** Synthesis of pyrrolizidinones by cyclization involving *N*-acyliminium ion intermediates.

entrance to six pyrrolizidine alkaloids [196], while cyclization of **181** led to the synthesis of (+)-heliotridine [197].

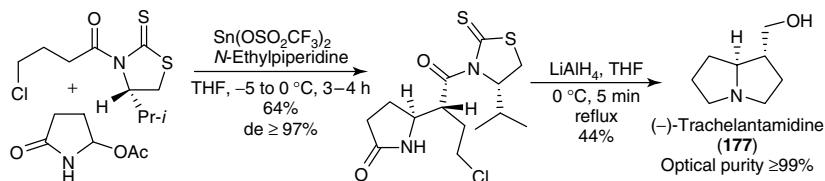
$\text{SmI}_2$ -mediated intramolecular reductive alkylation of tartarimide derivative **182** affords an easy approach to dihydroxylated pyrrolizidinone (Scheme 2.85) [198]. A similar product can be obtained through silylative Dieckmann-like cyclizations of ester-imides **183** (Scheme 2.85) [199].

A general 1,3-thiazolidine-2-thione-induced asymmetric  $\alpha$ -amidoalkylation-type reaction affords a two-step approach to (–)-trachelantamidine (**177**, Scheme 2.86) [200]. Using this strategy, Pilli *et al.* established a synthesis of (+)-hastanecine [201].

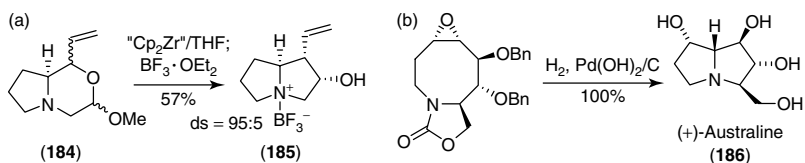
“ $\text{Cp}_2\text{Zr}$ ”-Mediated ring contraction of vinylmorpholine derivatives **184** was used to synthesize pyrrolidines and pyrrolizidine derivative **185**. The latter was further transformed into (–)-macronocine (Scheme 2.87a) [202]. In White's total synthesis of (+)-australine (**186**), a transannular cyclization was used to build the pyrrolizidine ring (Scheme 2.87b) [203].



**Scheme 2.85** Nucleophilic cyclizations leading to dihydroxylated pyrrolizidinone derivatives. ( $\text{Fe}(\text{DBM})_3$  = tris(dibenzoylmethido)iron(III)).



**Scheme 2.86** Nagao's approach to (–)-trachelantamidine.



**Scheme 2.87** Synthesis of pyrrolizidine by ring contraction and transannular cyclization reactions.

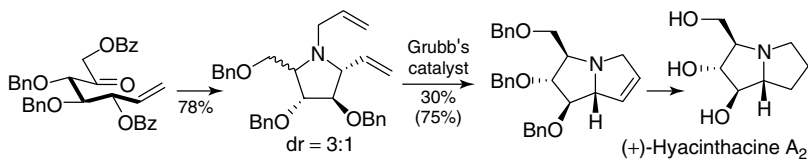
### 2.3.1.3 Asymmetric Synthesis of Polyhydroxylated Pyrrolizidines

By a combination of Nicotra's highly stereoselective vinylation, Ganem's pyrrolidine formation procedure [15], and the RCM reaction, Martin achieved the first synthesis of (+)-hyacinthacine A<sub>2</sub> (187) in six steps starting from protected D-arabinofuranose (9) (Scheme 2.88) [204].

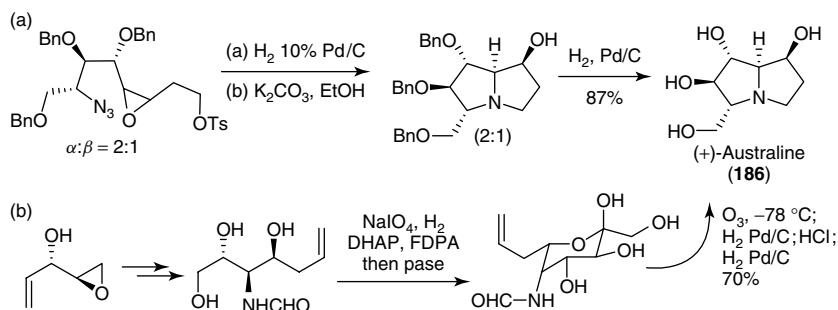
Reductive double cyclization is an efficient strategy for the synthesis of polyhydroxylated pyrrolizidines [53, 205, 206], as was demonstrated by Pearson *et al.* in their synthesis of (+)-australine (186) and (–)-7-*epi*-alexine (Scheme 2.89a) [205]. Another nice demonstration of the efficiency of the reductive double cyclization strategy was made by Wong and coworkers, in which a skillful combination of an improved Sharpless asymmetric epoxidation of divinylcarbinol (64) with Payne rearrangement, an enzymatic aldol reaction, and an intramolecular bis-reductive amination led to a concise synthesis of australine (186) (Scheme 2.89b) [53].

The Cope–House cyclization is a useful method for the construction of pyrrolidine rings. This strategy was used for the synthesis of pyrrolizidines 5-*epi*-hyacinthacine A<sub>3</sub> and 5-*epi*-hyacinthacine A<sub>5</sub> (Scheme 2.90) [207].

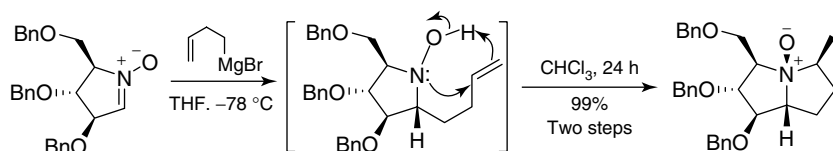
Besides serving as electrophiles in the nucleophilic addition with Grignard reagents, the umpolung of nitrones can be achieved by a samarium diiodide–induced coupling of nitrones with electron-deficient olefins. This paved the route for a very concise synthesis of (+)-hyacinthacine A<sub>2</sub> (187) (Scheme 2.91) [208].



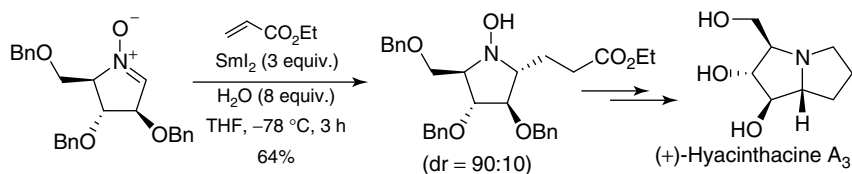
**Scheme 2.88** Martin's synthesis of (+)-hyacinthacine A<sub>2</sub>.



**Scheme 2.89** Pearson's and Wong's syntheses of (+)-australine. DHAP = dihydroxyacetone phosphate; FDPA = fructose-1,6-diphosphate aldolase; and Pase = acid phosphatase.



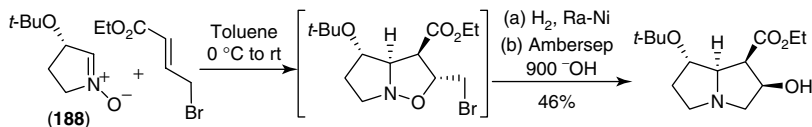
**Scheme 2.90** Py's synthesis of (+)-hyacinthacine  $A_2$ .



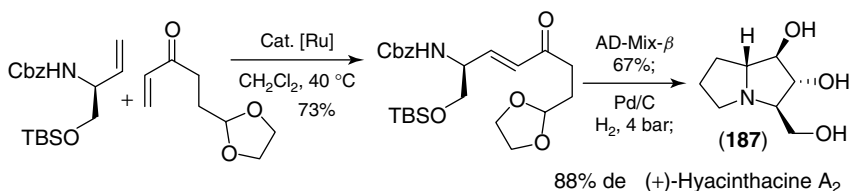
**Scheme 2.91** Py's synthesis of (+)-hyacinthacine  $A_3$ .

By regio- and diastereoselective 1,3-dipolar cycloaddition of functionalized dipolarphiles with pyrrolidine nitrones, several pyrrolizidines and indolizidines have been synthesized. For example, the 1,3-dipolar cycloaddition of nitron 188 with ethyl 4-bromocrotonate provided a highly selective and concise synthesis of (+)-heliotridine (Scheme 2.92) [209]. A similar strategy was also used in the synthesis of hyacinthacine  $A_2$  and 7-deoxycasuarine [210].

Bleichert's enantiospecific synthesis of (+)-hyacinthacine  $A_2$  (187) exhibits the efficiency of a convergent synthesis. Indeed, after synthesizing fragments A and B respectively, it needs only three steps to combine the two fragments and convert the coupled product into the target molecule hyacinthacine  $A_2$ , in which two rings and three chiral centers have been formed stereoselectively (Scheme 2.93) [211].



**Scheme 2.92** Brandi's synthesis of (+)-heliotridine.



**Scheme 2.93** Blechert's enantiospecific convergent synthesis (+)-hyacinthacine A<sub>2</sub>.

## 2.4

### Acknowledgments

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### 3

## Asymmetric Synthesis of Six-Membered Ring Heterocycles

*Naoki Toyooka*

### 3.1

#### Introduction

The functionalized six-membered heterocycles with one nitrogen (piperidine ring systems) have been found in many biologically and medically important natural and nonnatural products. Among the nitrogen heterocycles, the piperidine ring probably represents the more frequently encountered substructure of natural or unnatural products. Indeed, many methodologies for the asymmetric construction of this ring system have been developed. This chapter gathers the most recent methods described so far for the asymmetric access of these products, and is divided into four sections: dihydropyridines, tetrahydropyridines, monocyclic and carbocyclic fused piperidines and finally fused tri- or bicyclic systems with bridgehead nitrogen. The first two sections describe the preparation of unsaturated systems that are often used as intermediates in the syntheses of piperidines, thus the methods reported in these two sections may also be useful for the synthesis of piperidines. Owing to the very important literature and several available reviews [1] on this topic, only the recent literature from 2000 to 2007 is reviewed.

### 3.2

#### Dihydropyridines

The main interest of dihydropyridine compounds is their reactivity. They can be transformed to yield highly functionalized and substituted piperidines. Indeed, there are quite unstable products and, of course, there are, in most of the cases, intermediates in the asymmetric synthesis of piperidine derivatives. Thus, the preparation of dihydropyridines should be considered as supplementary methods to attain the saturated piperidine compounds.

Direct addition of nucleophile on pyridine ring in an enantioselective manner is one of the most effective methods for the construction of chiral six-membered

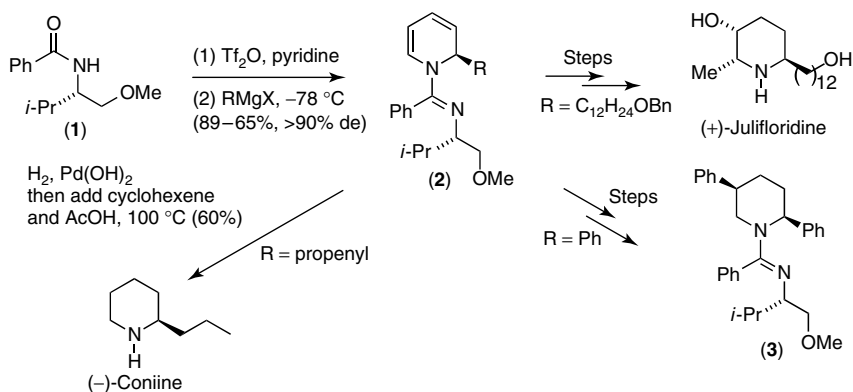


ring system. The pioneering work on this area was reported from Comins' group [2]. This was the method that Charette used to elaborate a practical and highly regio- and stereoselective synthesis of 2-substituted dihydropyridine. The strategy involved the addition of Grignard reagents to chiral pyridinium salt prepared from **1** and pyridine in the presence of  $\text{TiF}_2\text{O}$  to yield the 2-substituted dihydropyridines. These compounds are valuable synthetic intermediates since an enantioselective synthesis of (–)-coniine was obtained by this methodology in very few steps [3]. Owing to the other application of this method to natural product synthesis, the expedient asymmetric synthesis of (+)-julifloridine in four steps was achieved from **2** ( $\text{R}=\text{C}_{12}\text{H}_{24}\text{OBn}$ ) by monohydrogenation followed by a one-pot, highly diastereoselective epoxidation–nucleophilic addition of  $\text{Me}_2\text{Zn}$ . On the other hand, synthesis of the nonracemic 2,5-*cis*-disubstituted piperidine **3** has also been accomplished (Scheme 3.1) [4].

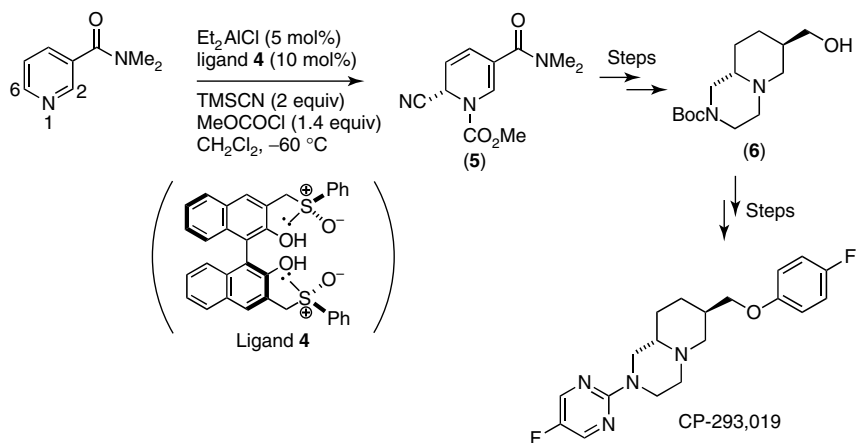
The first catalytic asymmetric addition reaction of nucleophile to *N*-acylpyridinium ion was reported by Shibasaki and Kanai using Lewis acid–Lewis base bifunctional asymmetric catalyst. Thus, the catalytic enantioselective Reissert reaction of pyridine was achieved in the presence of chiral ligand **4** (10 mol%) and  $\text{Et}_2\text{AlCl}$  (5 mol%) to yield the adduct **5** (98% yield with 91% ee). Interestingly, the use of **4**, which is not  $\text{C}_2$  symmetric, showed best regio- (1,6- vs. 1,2-; 12:1–50:1) and enantioselectivity (up to 96% ee) on this reaction. Adduct **5** was converted to the key intermediate **6** for the synthesis of dopamine  $\text{D}_4$  receptor-selective antagonist CP-293,019 (Scheme 3.2) [5].

Ma's group also reported the catalytic enantioselective addition of activated terminal alkynes to 1-acylpyridinium salts using Cu-bis(oxazoline) complexes. Among the chiral bis(oxazoline) catalysts, use of less bulky ligand **7** showed best results, and two adducts **8** and **9** were obtained with 94% and 91% ee, respectively. Both adducts were converted to poison-frog alkaloids **167B** and **223AB**, respectively, as shown in Scheme 3.3 [6].

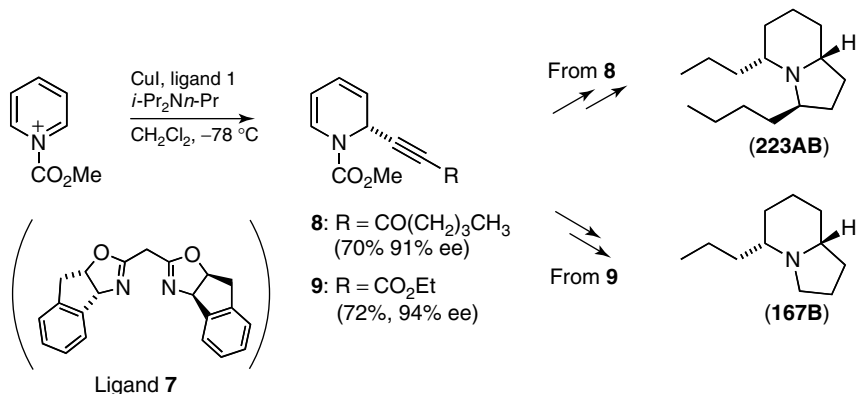
Yamada reported the synthesis of chiral 1,4-dihydropyridines by face-selective addition to a cation- $\pi$  complex of a pyridinium salt. The addition reaction of ketene



Scheme 3.1



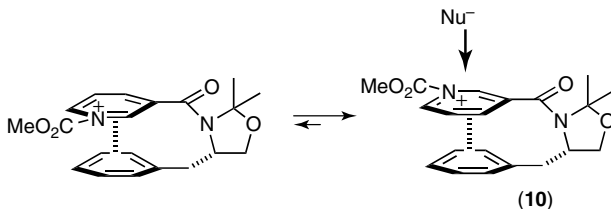
Scheme 3.2



Scheme 3.3

silyl acetals to the pyridinium salt of nicotinic amide derivatives proceeded in good diastereoselectivity to yield the 1,4-dihydropyridine derivatives. The nucleophile attacked on more stable conformer **10** (from *ab initio* calculations) from less hindered top face to yield the product (Scheme 3.4) [7].

The strategy of Comins was broadened by his author with the highly regio- and diastereoselective addition of several nucleophiles such as Grignard reagents, lithium acetylide, and metallo enolates to chiral *N*-acylpyridinium salts to give enantiopure *N*-acyl-2,3-dihydro-4-pyridones. According to this methodology, the first asymmetric synthesis of natural (+)-cannabistatine [8] from **11**, a concise asymmetric synthesis of (+)-allopumiliotoxin **267A** [9] from **12**, the asymmetric synthesis of (+)- $\beta$ -conhydrine [10] from **13**, and synthetic studies toward (–)-FR901483 [11] from **14** have been reported as shown in Scheme 3.5.



### Scheme 3.4

### 3.3

## Tetrahydropyridines

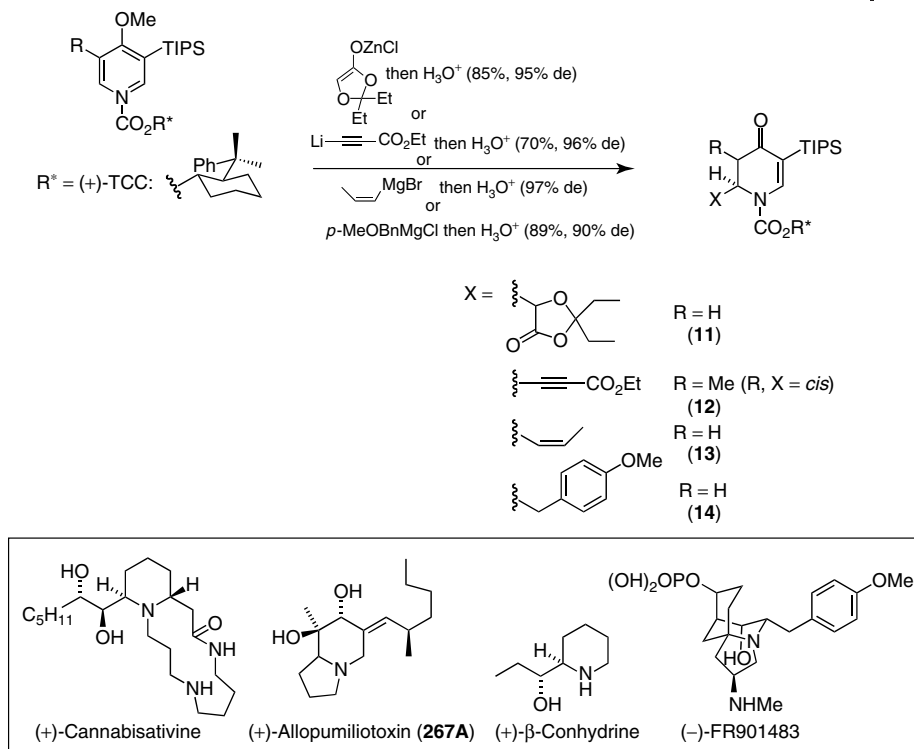
Tetrahydropyridines are more stable compounds than dihydropyridines, but, as dihydropyridines, are mainly prepared as intermediates in the synthesis of piperidines. The position where the unsaturation takes place is important: the 1,2,3,4-tetrahydropyridines are enamines that can react at the C-3 position with electrophiles giving access to more substituted compounds.

Though several methods were described for the construction of substituted tetrahydropyridines, the most versatile methodology is probably the ring-closing metathesis (RCM), which has emerged as one of the most powerful tools in organic synthesis. The total synthesis of piperidine and pyrrolidine natural alkaloids with RCM as a key step has been reviewed by Lebreton in 2003 [12].

### 3.3.1

## Ring-Closing Metathesis (RCM)

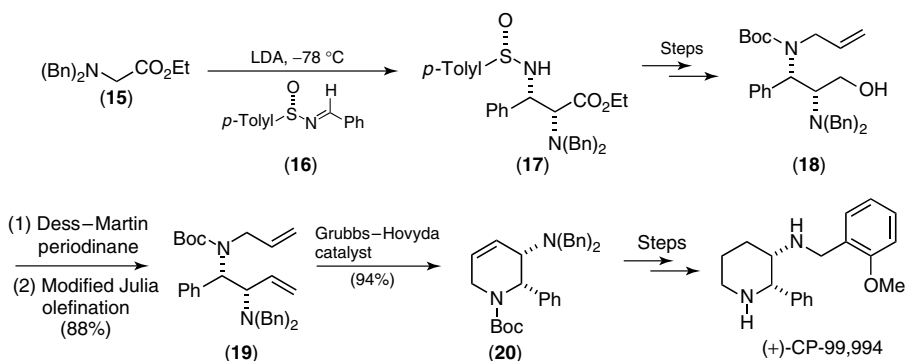
Davis reported the asymmetric synthesis of (+)-CP-99,994 by using the RCM reaction of diene **19**, derived from sulfinimine-derived 2,3-diamino ester **17**. Thus, the addition reaction of enolate of **15** to chiral sulfinamide **16** yielded the differentially *N*-protected diamino ester **17**. The latter was converted to alcohol **18**, which was then transformed into **19**. The RCM reaction of **19** using Grubbs–Hoveyda catalyst



Scheme 3.5

yielded tetrahydropyridine **20** in high yield, which was converted to (+)-CP-99,994 in four-step sequence (Scheme 3.6) [13].

Lebreton achieved the chiral synthesis of (–)-3-epi-deoxoprosopinine by using chiral imino alcohol **21** and compound **23**. The diastereoselective allylation of **21** yielded the *trans*-adduct **22** as the major product and subsequent RCM reaction of



Scheme 3.6

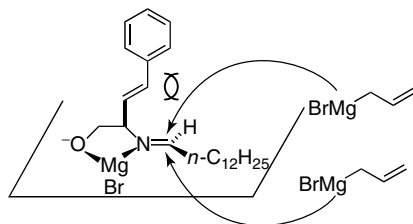
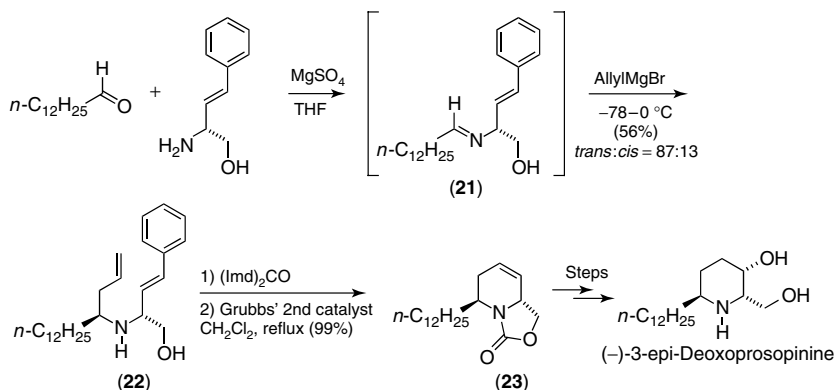


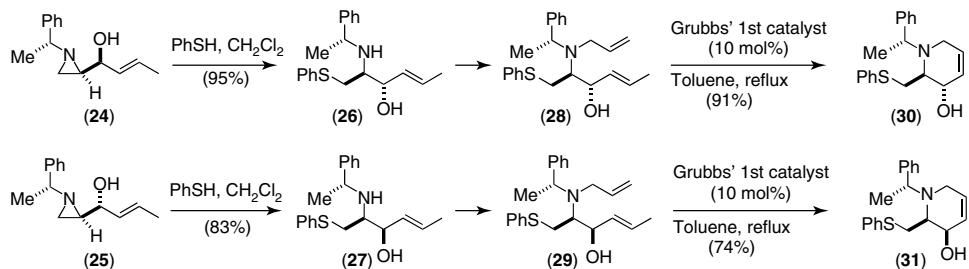
Fig. 3.1 Stereochemical course of Grignard addition to **21**.



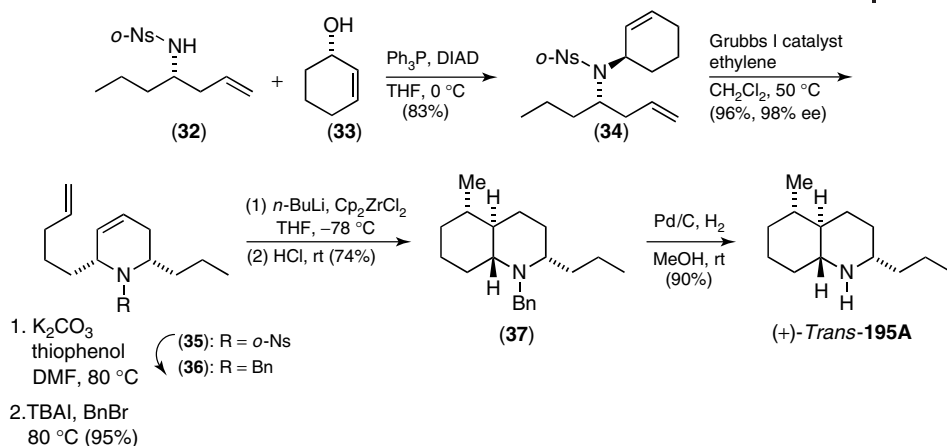
Scheme 3.7

oxazolizinone yielded **23**. The diastereoselectivity of the above addition is explained by the chelation-controlled model shown in Figure 3.1. Epoxidation of **23**, reductive opening of the epoxide followed by alkaline hydrolysis of the oxazolizinone ring, yielded (–)-3-epi-deoxoprosopinine (Scheme 3.7) [14].

In the Lee's chiral synthesis of tetrahydropyridines, the dienes required for the RCM were prepared via the regioselective opening of the chiral aziridine ring systems as the key step. Both chiral aziridines **24** and **25** were treated with PhSH to yield the amino alcohol **26** or **27** in highly regioselective manner, which was converted to tetrahydropyridines **30** or **31** via dienes **28** or **29**, respectively (Scheme 3.8) [15].



Scheme 3.8



Scheme 3.9

An interesting ring-rearrangement metathesis was developed by Blechert in the total synthesis of poison-frog alkaloid (+)-*trans*-195A. Thus, the Mitsunobu reaction of the chiral sulfonamide **32** with chiral cyclohexenol **33** yielded the secondary amide **34**, which was subjected to ring-rearrangement metathesis using Grubbs I catalyst to yield **35**. The protecting group on nitrogen in **35** was crucial to achieve the next Negishi-coupling reaction. Negishi-coupling reaction of the *N*-benzyl derivative **36** proceeded smoothly to yield **37**, which was converted to (+)-*trans*-195A (Scheme 3.9) [16].

### 3.3.2

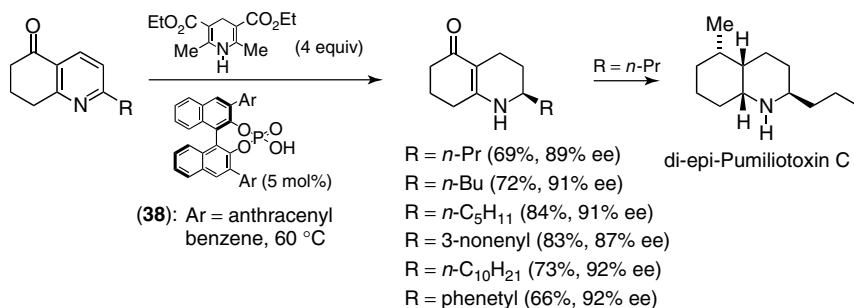
#### Reduction of Pyridine Derivatives

The chiral Brønsted acid-catalyzed reduction of pyridine derivatives is also an efficient method to prepare tetrahydropyridines or octahydroquinolinones in good ee. Thus, the reduction of several pyridine derivatives, shown below, in the presence of chiral Brønsted acid **38** (5 mol%) and Hantzsch diethyl ester (4 equiv) as the hydride source yielded the reduction products in good ee. This methodology was applied to formal enantioselective synthesis of di-*epi*-pumiliotoxin C (Scheme 3.10) [17].

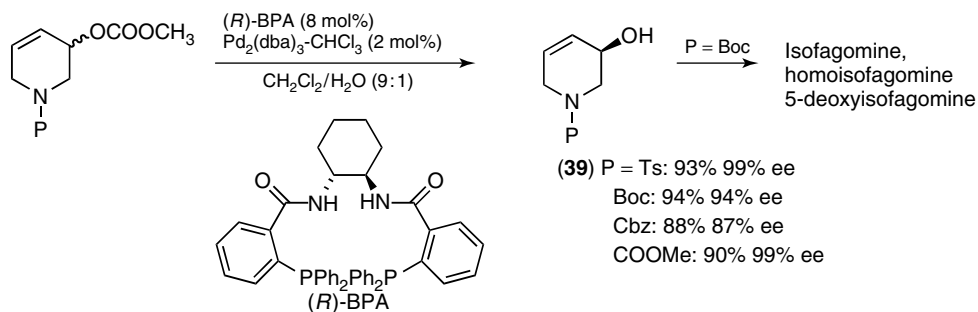
### 3.3.3

#### Deracemization Processes

Takahata reported the asymmetric synthesis of tetrahydropiperidinol chiral building block **39** using the palladium-catalyzed deracemization of corresponding carbonate (Scheme 3.11) [18]. Thus, the reaction was performed using 8 mol% of phosphine ligand ((*R*)-BPA) developed by Trost and 2 mol% of  $\text{Pd}_2(\text{dba})_3$  in  $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$  (9:1) to yield **39** (88–94% yield and 87–99% ee), which is the key chiral building block for the synthesis of biologically important alkaloids such as 1-azasugars [19].



Scheme 3.10



Scheme 3.11

## 3.3.4

## Michael Addition Followed by Elimination

The synthesis of tetrahydropyridines using the diastereoselective intramolecular Michael cyclization of vinylsulfinyl-containing amino alcohol as the key step, as shown in Scheme 3.12, was described by Delgado. The authors designed a “one-pot” procedure based on the removal of *N*-Boc followed by neutralization with excess Et<sub>3</sub>N and “in situ” cyclization under high-dilution conditions at 50 °C to yield the piperidine **40** or indolizidine **41** with high diastereoselectivity. Elimination of the sulfoxide group yielded the tetrahydropyridines **42** or **43**, respectively [20].

Davis used the intramolecular Michael-type addition reaction followed by retro-Michael elimination reaction of the *N*-sulfinyl  $\delta$ -amino  $\beta$ -keto phosphonate to yield dihydropyridone **44** (Scheme 3.13). The conjugate addition reaction of **44** resulted in the selective formation of 2,6-*trans*-disubstituted tetrahydropyridine **45**, which was used for asymmetric synthesis of (–)-myrtine [21].

## 3.3.5

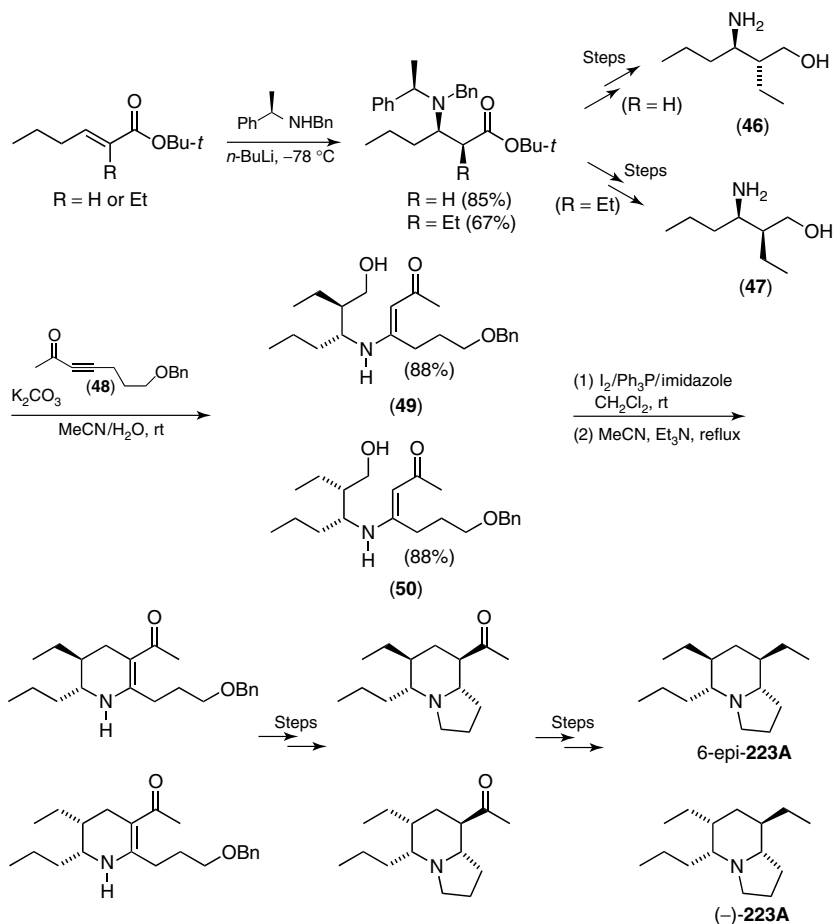
## Enamine Reaction

The intramolecular enamine reaction in the electrophilic center was used by several groups to prepare the piperidine ring through the C3–C4 bond formation. In the



synthesis of indolizidine alkaloid, Ma reported the efficient construction of the functionalized cyclic enamines by the Michael addition of enantiopure amino alcohols to alkynones followed by intramolecular cyclization reaction. On the basis of this methodology, the asymmetric syntheses of poison-frog alkaloid (–)-**223A** and its 6-epimer [22], (–)-deoxoprosopphylline [23], and (–)-deoxocassine and (+)-azimic acid [24] have been achieved. The enantiopure amino alcohols **46** and **47** were prepared by Davies' method [25], and were added to alkynone **48** by Michael



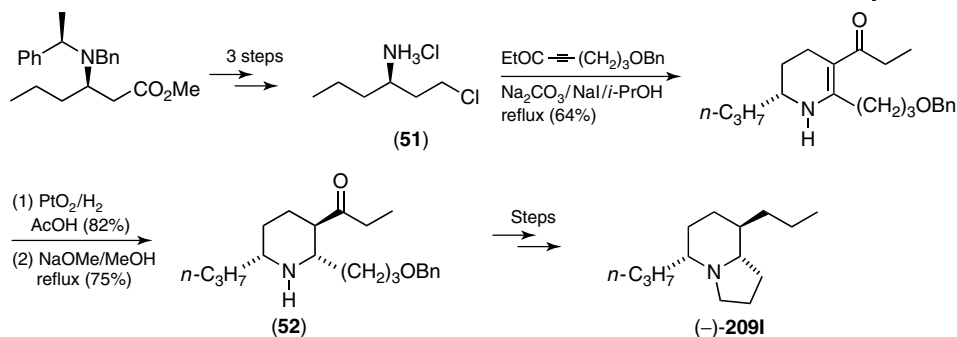


Scheme 3.14

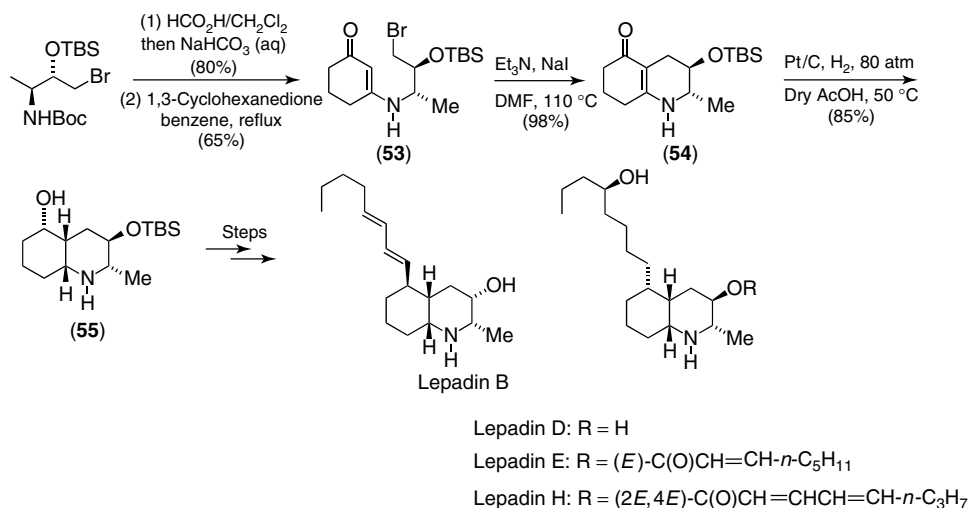
addition reaction to yield the enamines **49** and **50**, respectively. The key two-step cyclization of **49** or **50** yielded the cyclic enaminones, which were converted to 6-epi-**223A** (originally proposed structure for natural **223A**) [26] and (–)-**223A** by modifications on the side chain, reduction of the ketone moiety, and indolizidine formation reaction (Scheme 3.14).

This methodology was developed to one-pot procedure, and then the enantioselective total synthesis of the poison-frog alkaloid (–)-**209I** has been achieved. The key one-pot reaction was performed by the reaction of chloride **51** with conjugated alkyne to yield the piperidine (**52**) after hydrogenation and epimerization at the 3-position, which was converted to (–)-**209I** in some steps (Scheme 3.15) [27].

The total synthesis of lepadins B, D, E, and H and determination of the absolute configuration of lepadins D, E, and H were also achieved by Ma using the same methodology. The key feature of Ma's synthesis was the construction of octahydro



Scheme 3.15



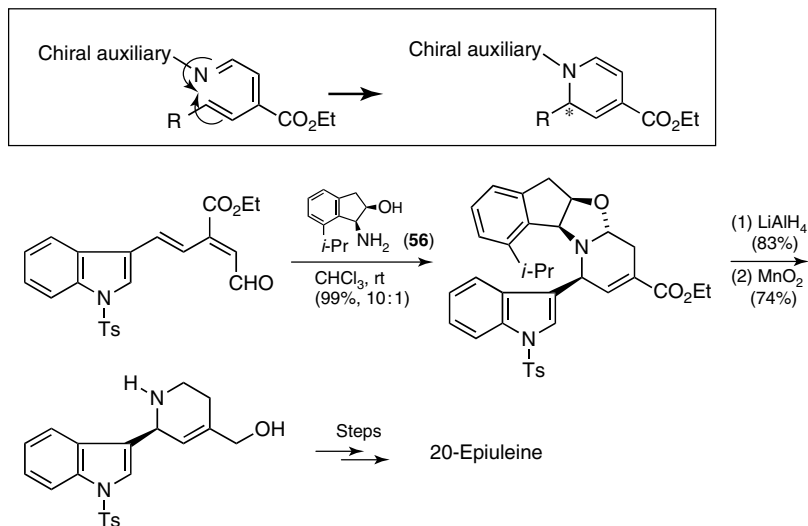
Scheme 3.16

quinolinone ring system by alkylative cyclization of **53**. The diastereoselective hydrogenation of **54** was performed in the presence of Pt/C catalyst by a stereoelectronically controlled axial addition of hydrogen to yield the common intermediate **55** for the synthesis of lepadins after Boc protection and oxidation of the hydroxyl group of the resulting amino alcohol. Elaborations on **55** yielded lepadins B, D, E, and H. The absolute configuration of later three alkaloids was determined by these total syntheses (Scheme 3.16) [28, 29].

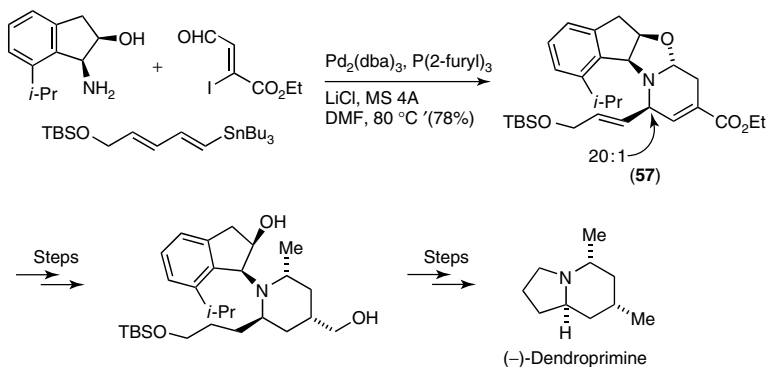
### 3.3.6

#### Electrocyclization

Katsumura reported the asymmetric 6 $\pi$ -azaelectrocyclization utilizing the 7-alkyl substituted *cis*-1-amino-2-indanols **56** as the novel chiral auxiliary. Then the method



Scheme 3.17

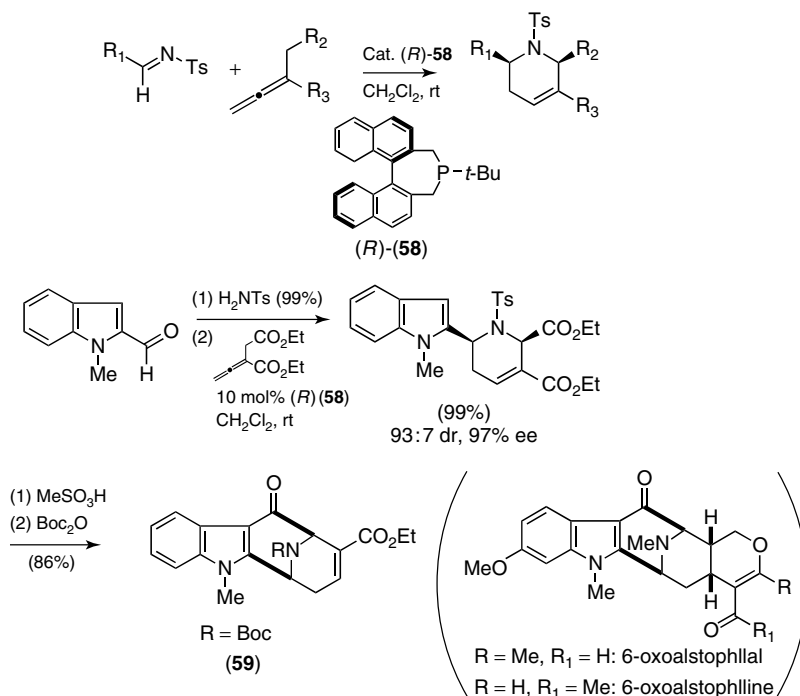


Scheme 3.18

was successfully applied to the asymmetric formal synthesis of 20-epiuleine (Scheme 3.17) [30].

Furthermore, efficient one-pot process of the above reaction has been developed by the same author [31]. Thus, the unsaturated ester **57** was synthesized by this method, and the asymmetric synthesis of (-)-dendroprimine was achieved via the stereoselective opening of the *N*, *O*-acetal as shown in Scheme 3.18 [32].

Fu achieved the elegant catalytic asymmetric [4 + 2] annulation of imines with allenes in the presence of the catalytic amounts of binaphthyl-based  $C_2$ -symmetric phosphine **58** (5–10 mol%) to yield 2,6-*cis*-disubstituted piperidine derivatives in good ee (Scheme 3.19). This methodology was applied to the synthesis of a framework (**59**) common to an array of important natural products such as the indole alkaloids of 6-oxaalstophyllal and 6-oxaalstophylline [33].



Scheme 3.19

### 3.4 Monocyclic Piperidines and Carbocyclic Fused Systems

#### 3.4.1

##### Generalities

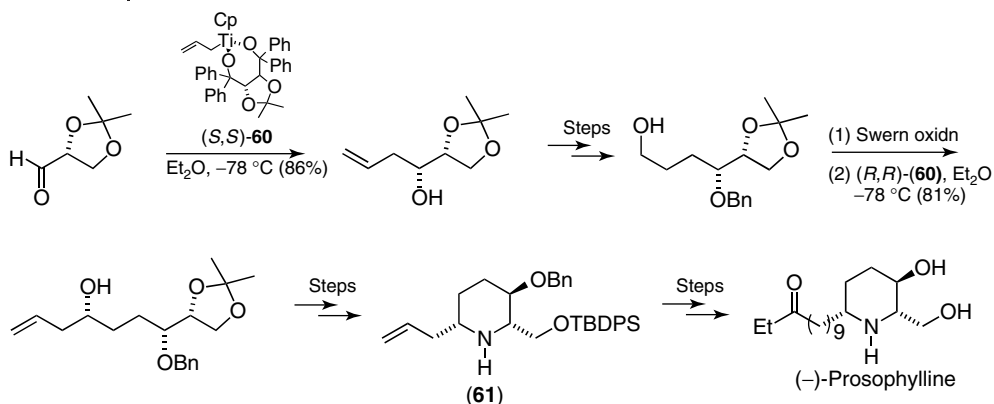
In this section, the asymmetric synthesis of piperidines and their corresponding carbocyclic fused systems are described. Of course, most of the methods described above for the preparation of di- and tetrahydropyridines could be applied to piperidines after functionalization or reduction.

The following section deals with different cyclization methods, cycloaddition, ring transformation, and substitution of already formed heterocycles.

#### 3.4.2

##### Cyclization Methods

Several types of substituted monocyclic piperidines have been synthesized. The more classic cyclization method and more often used is nitrogen intramolecular substitution reaction of appropriate precursors to form the cyclized products in chiral form. Nevertheless, other methods forming the C–C bonds are also reported and described below.



Scheme 3.20

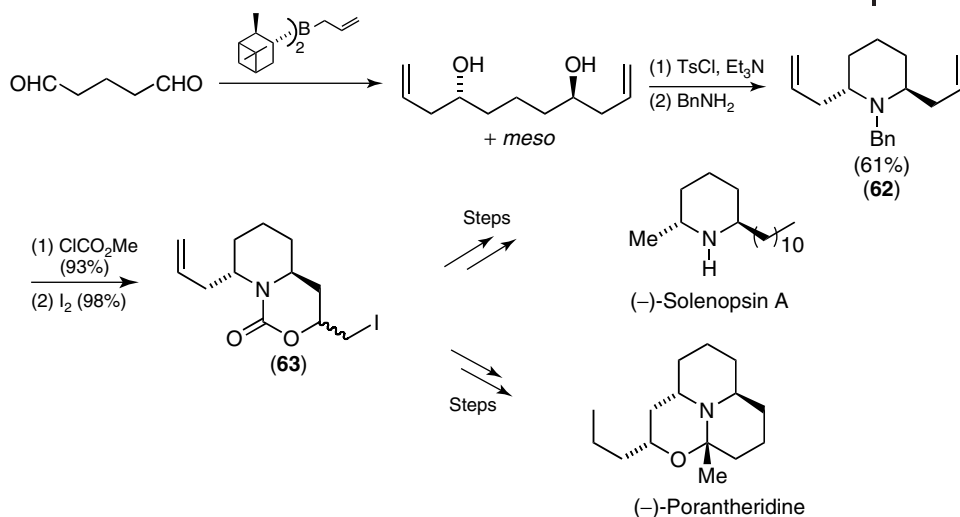
#### 3.4.2.1 Nitrogen as a Nucleophile

**S<sub>N</sub>2 Reactions** The nucleophilic substitution with nitrogen as the nucleophile is probably the most obvious method to achieve cyclization; the leaving group may be an activated ester (tosylate), epoxide, or a halogen as illustrated in the following examples. Cossy reported the sequential use of enantioselective allyltitanation using the both enantiomers of **60** to form the chiral homo-allyl alcohol, which was converted to the chiral 2,3,6-trisubstituted piperidine **61** by intramolecular cyclization reaction of the chiral allylamine. Construction of the side chain by Grubbs 2nd catalyst-catalyzed cross-metathesis reaction yielded (–)-prosophylline (Scheme 3.20) [34].

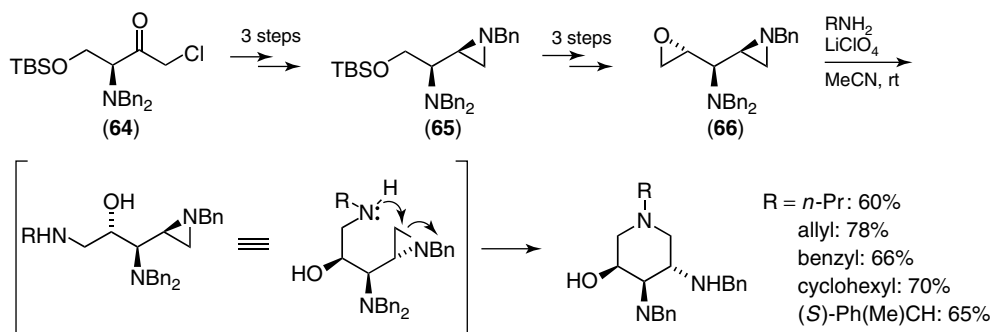
The double nucleophilic attack of nitrogen on a bis-tosylate or a bis-epoxide was also described. Takahata reported the synthesis of a novel C<sub>2</sub>-symmetric 2,6-diallylpiperidine building block for the synthesis of several alkaloids using the double asymmetric allylation under the Brown procedure and cyclization by inter- and intramolecular substitution with benzylamine to yield the key piperidine **62**. Desymmetrization of **62**, crucial step for further elaboration of this building block, was achieved by the intramolecular iodocarbamation to yield the oxazolizinone **63** in high yield. This oxazolizinone is a versatile chiral building block for the synthesis of several alkaloids such as (–)-solenopsin A and (–)-porantheridine, as shown in Scheme 3.21 [35].

Concellon and Rivero achieved the chiral synthesis of 3,4,5-trisubstituted piperidine by sequential inter- and intramolecular ring opening reaction of epoxyaziridine with primary amines as the key step (Scheme 3.22). The aminoketone **64**, derived from L-serine, was converted to aziridine **65** in three steps. The aziridine was transformed into desired epoxyaziridine **66** in three-step sequence, and the key opening reaction of **66** with several primary amines in the presence of lithium perchlorate yielded the 3,4,5-trisubstituted piperidines as the sole product [36].

Gallagher reported [3 + 3] annulation using the 1,3-cyclic sulfate as a double electrophile in the asymmetric synthesis of piperidine. The chiral 1,3-diol was converted to cyclic sulfate, which was treated with dianion of **67** to yield the



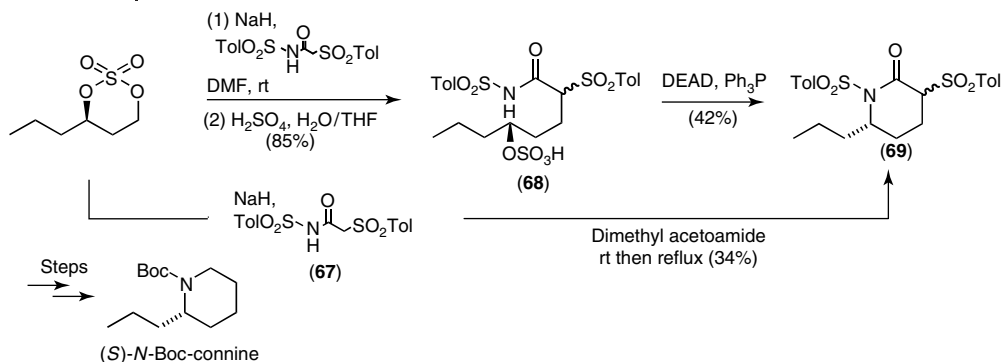
Scheme 3.21



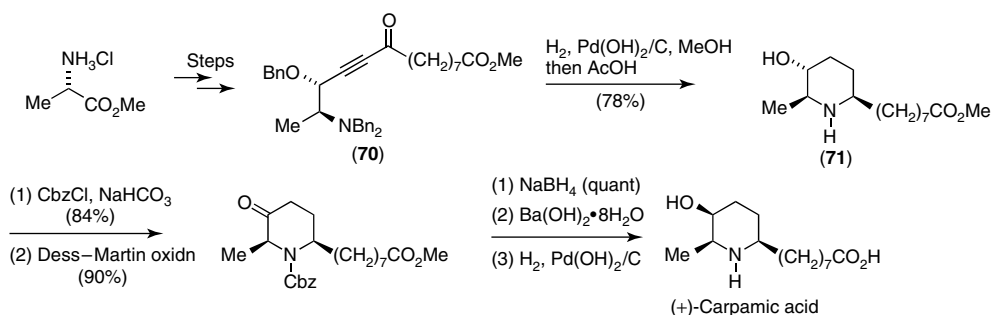
Scheme 3.22

piperidone **69** directly or via sulfate **68**. This piperidone was transformed into (*S*)-coniine in several steps (Scheme 3.23) [37].

**Reductive Alkylation** Efficient cyclization reactions via the formation of iminium ion followed by its reduction to form the substituted piperidines have been achieved. Mori described the chiral synthesis of (+)-carpamic acid by stereoselective hydrogenation of the iminium, generated from an acyclic amino ketone, to give 2,6-*cis*-disubstituted 3-piperidinol derivative. The key substrate **70** was synthesized from (*S*)-alanine methyl ester involving the diastereoselective addition of the acetylene unit to the corresponding aldehyde. Treatment of **70** with Pearlman's  $\text{Pd}(\text{OH})_2$  in methanol yielded the piperidine **71**, which was converted to (+)-carpamic acid (Scheme 3.24) [38].



Scheme 3.23

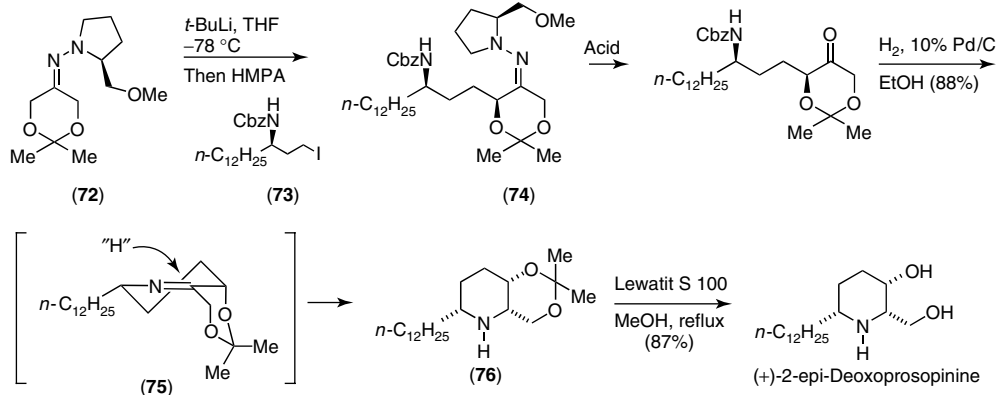


Scheme 3.24

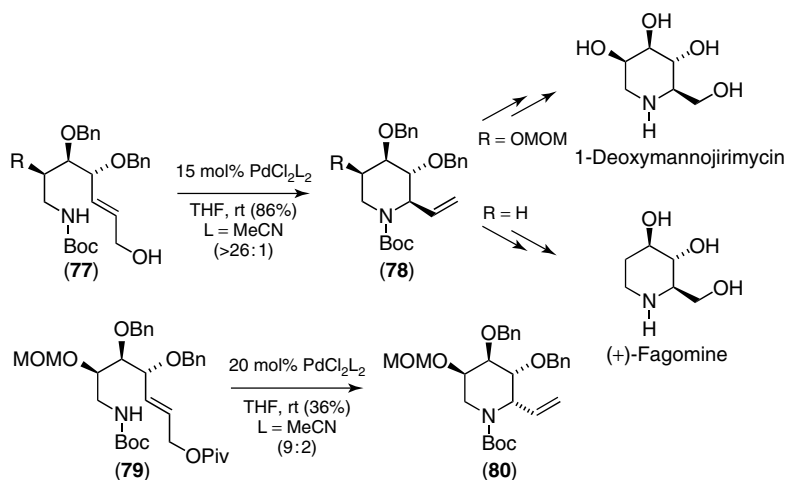
Kumar's [39], Ghosh's [40], and Hum's [41] groups also used the similar iminium cyclization–reduction process to yield 2,6-*cis*-disubstituted 3-piperidinol derivatives for the chiral synthesis of (–)-deoxocassine, (+)-carpamic acid, and (+)-spectaline.

Enders' group reported the asymmetric total synthesis of (+)-2-*epi*-deoxyprosopinine by using his original SAMP/RAMP hydrazone method as the key step. The  $\alpha$ -alkylation of SAMP hydrazone **72** with iodide **73**, which was also prepared by SAMP method, yielded the product **74** with high diastereoselectivity (*de* = 95%). Hydrolytic cleavage of the auxiliary followed by hydrogenolysis of Cbz-group and subsequent reductive amination resulted in an attack of hydrogen from sterically less hindered *si* face of resulting imine **75** to yield the piperidine **76**. Finally, deprotection of acetonide group yielded (+)-2-*epi*-deoxyprosopinine, as shown in Scheme 3.25 [42].

**$\pi$ -Allyl Substitution** The metal-catalyzed cyclization reactions involving a  $\pi$ -allyl metal have also been used by several groups to form the six-membered nitrogen heterocycles. For instance, Hirai achieved the enantioselective synthesis of azasugars of 1-deoxymannojirimycin [43] and fagomine [44] using his original Pd(II)-catalyzed cyclization of urethanes **77** to form the functionalized piperidine ring systems **78** as the key step. Interestingly, the use of the bulky pivaloyl ester



Scheme 3.25



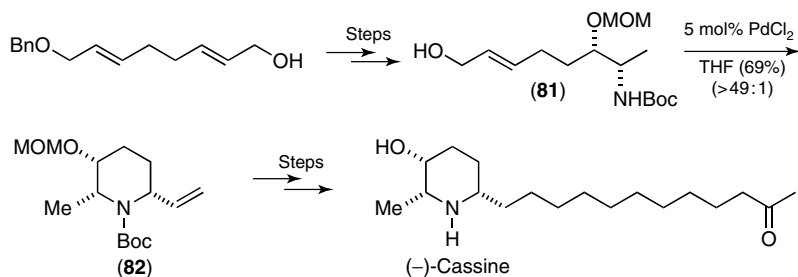
Scheme 3.26

**79**, instead of allylic alcohol **77**, for the cyclization reaction resulted in the selective formation of the diastereomer **80** (9:2) (Scheme 3.26).

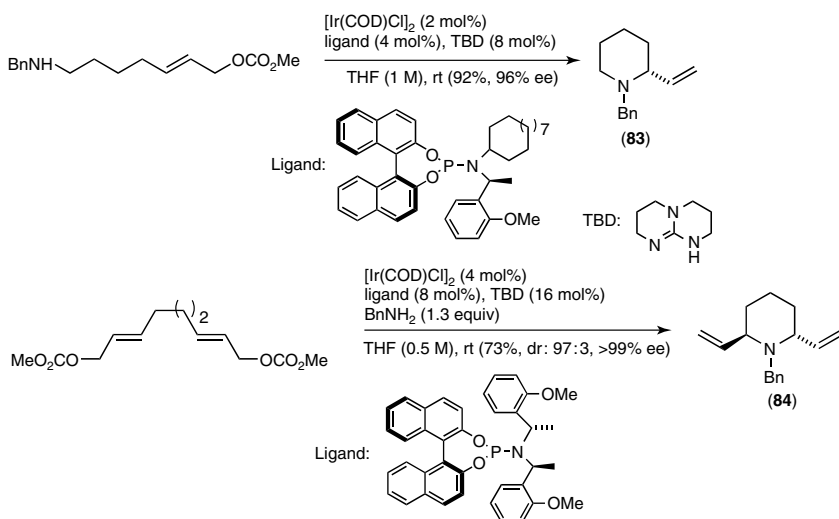
Makabe used the Pd(II)-catalyzed cyclization of amino allylic alcohol, originally developed by Hirai [45], to obtain 2,6-*cis*-disubstituted 3-piperidinol derivative (Scheme 3.27). Thus, the treatment of allylic alcohol **81** with 5 mol% of PdCl<sub>2</sub> yielded the 2,6-*cis*-disubstituted 3-piperidinol **82** in a highly diastereoselective manner, which was transformed into (–)-cassine [46].

Palladium was not the only used metal for such transformation; Helmchen's group developed the highly enantioselective synthesis of  $\alpha$ -vinyl substituted piperidine **83** by Ir-catalyzed allylic amination. This methodology was extended to sequential reaction to yield the C<sub>2</sub>-symmetric 2,6-*trans*-divinylpiperidine **84** with an excellent ee (Scheme 3.28) [47].



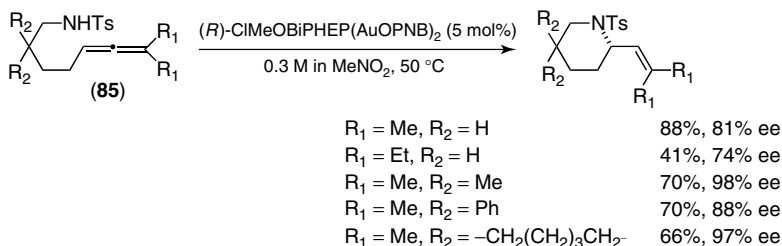


Scheme 3.27

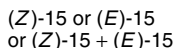


Scheme 3.28

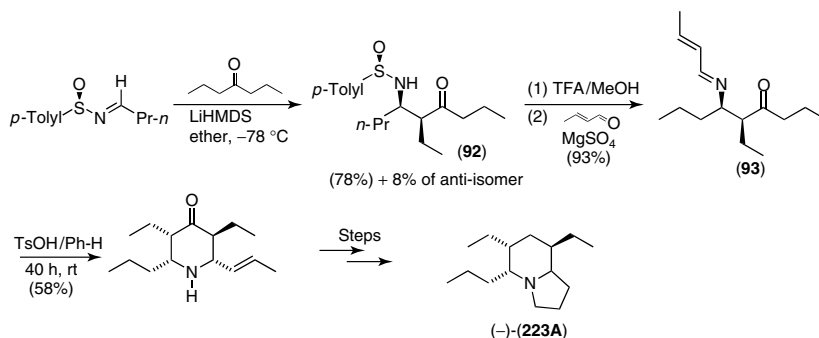
**Hydroamination of Allenes** The gold(I)-catalyzed intramolecular hydroamination of allenes **85** was used by Toste for the preparation of chiral piperidines. Chiral ligands allowed the reaction to occur with good enantioselectivity (74–98% ee), as shown in Scheme 3.29. A dramatic amplification of enantioselectivity was observed when benzoate counterions were employed in this cyclization reaction [48].



Scheme 3.29



Scheme 3.31



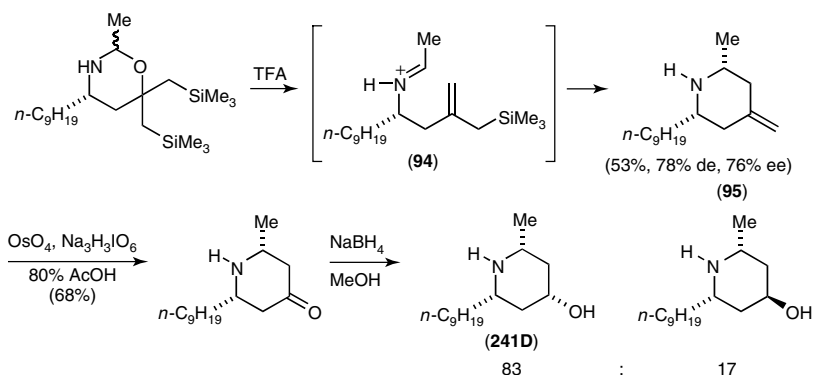
Scheme 3.32

the synthesis of several alkaloids, and the asymmetric syntheses of (–)-**223A** [51], (–)-nupharamine [52], and (+)-**241D** [53] have been achieved. The first key reaction was the *syn*-selective addition of the enolate to chiral sulfinimine to yield the  $\alpha$ -substituted  $\beta$ -amino ketone **92**. The second key step was the acid-catalyzed Mannich cyclization of **93**, derived from **92**, to yield the functionalized 4-piperidone, which was converted to (–)-**223A** by indolizidine formation followed by the reduction of the ketone moiety (Scheme 3.32).

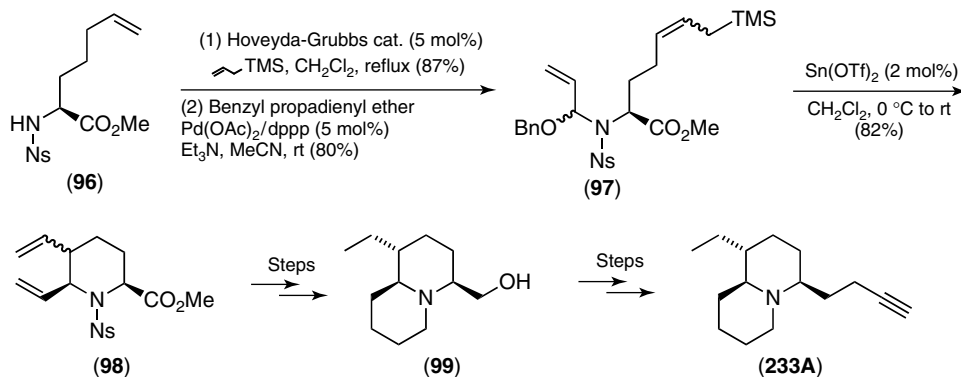
The intramolecular attack of allylsilane on iminium ion or imine is also effective to construct the chiral piperidine ring system by cyclization reaction.

Remuson described a new asymmetric synthesis of 2,6-*cis*-disubstituted 4-methylenepiperidine **95** based upon a Mannich-type intramolecular cyclization of an allylsilane on an iminium ion **94**. According to this strategy, the poison-frog alkaloid **241D** was synthesized, as shown in Scheme 3.33 [54].

Hiemstra and Rutjes investigated the amidopalladation of alkoxyallenes to yield the  $\alpha$ -alkoxycarbamates or amides. The formal enantioselective synthesis of poison-frog alkaloid **233A** has been achieved by using the above key reaction followed by acyliminium cyclization of the resulting  $\alpha$ -alkoxycarbamate. Treatment of **96** with Hoveyda–Grubbs catalyst (5 mol%) resulted in unusual double bond



Scheme 3.33



Scheme 3.34

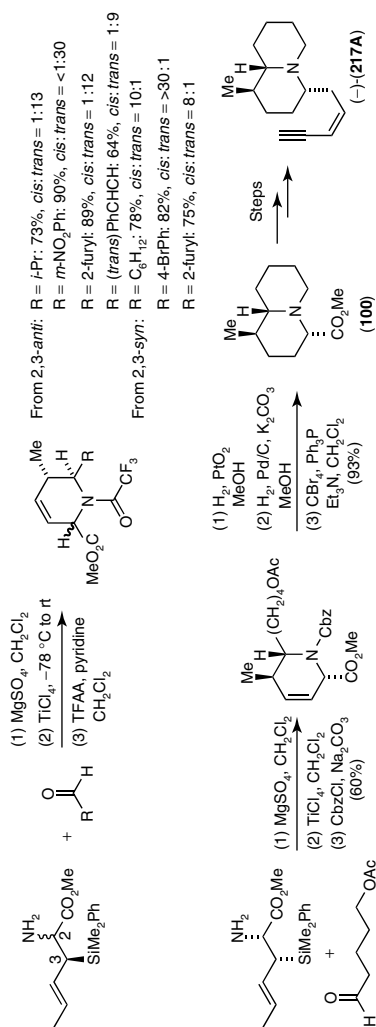
isomerization followed by cross-metathesis with allyltrimethylsilane to give the product, which was subjected to key amidopalladation with benzyl propadienyl ether to yield **97**.  $\text{Sn(OTf)}_2$ -catalyzed cyclization of **97** via acyliminium salt yielded the trisubstituted piperidine **98** as a 86:14 mixture of *trans/cis*-isomers. The major *trans*-isomer was converted to quinolizidine **99**, which is a key intermediate for the synthesis of poison-frog alkaloid **233A** (Scheme 3.34) [55].

The divergent synthesis of both 2,6-*cis*- and *trans*-3-*trans*-trisubstituted tetrahydropyridines from chiral organosilanes was reported by Panek. The first enantioselective total synthesis and determination of absolute stereochemistry of poison-frog alkaloid (–)-**217A** were achieved by this methodology via the quinolizidine **100**, as shown in Scheme 3.35. Treatment of preformed imine with  $\text{TiCl}_4$  at low temperature yielded the desired product with good-to-excellent diastereoselectivity (8:1 to >30:1). Interestingly, the *cis*–*trans* selectivity depended upon the chirality of organosilane. Use of the 2,3-*anti*-organosilanes yielded the 2,6-*trans* products as the major isomer (9:1 to >30:1); on the other hand, use of the 2,3-*syn*-organosilanes yielded the 2,6-*cis* products (8:1 to >30:1) selectively [56].

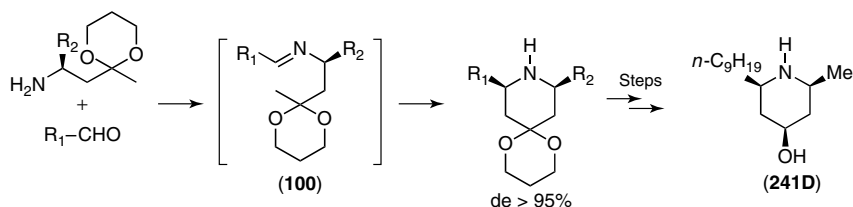
Troin's group investigated very actively on the intramolecular Mannich-type cyclization reaction of chiral imine **101** to yield the 2,6-*cis*-disubstituted piperidine ring systems. This reaction was applied to the syntheses of highly substituted piperidines [57], pipecolic acid derivatives [58], and (±)-alkaloid **241D** (Scheme 3.36) [59].

**Radical Cyclization** The construction of chiral piperidines by means of radical cyclization reaction is a very interesting method, although very rarely used.

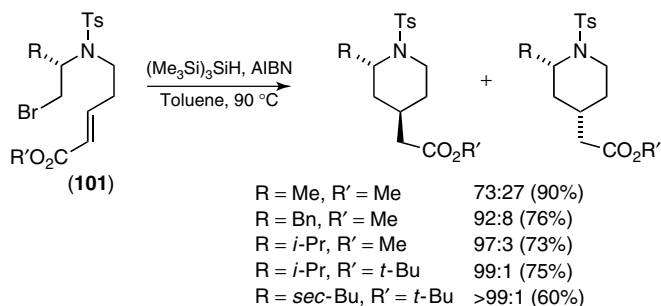
Snaith proposed a novel approach to 2,4-*trans*-disubstituted piperidines by the radical cyclization of 7-substituted 6-aza-8-bromooct-2-enoates **101** (Scheme 3.37) [60]. The use of tris(trimethylsilyl)silane instead of tributyltin hydride as the radical source enhanced the diastereoselectivity (>99:1). The *trans* selectivity is explained by the proposed transition state, as shown in Figure 3.2 involving a pseudo- $\text{A}^{1,3}$  allylic strain.



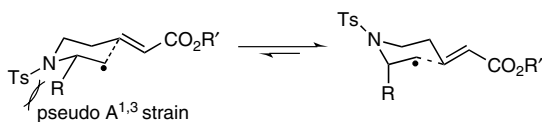
Scheme 3.35



Scheme 3.36



Scheme 3.37

Fig. 3.2 Preferential conformer on the radical cyclization of **101**.

## 3.4.3

## Cycloaddition Methods

## 3.4.3.1 [4 + 2] Azadiene Cycloaddition

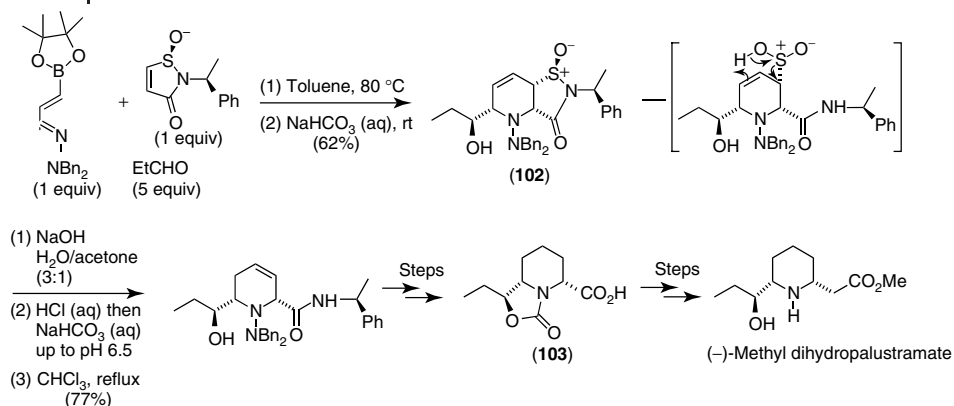
The construction of chiral piperidines by using the aza[4 + 2] cycloaddition reaction as the key steps has been reported.

Hall's group achieved a new entry to palustrine alkaloids using the three-component sequential, aza[4 + 2] cycloaddition/allylboration/retro-sulfinyl-ene, reaction (Scheme 3.38). This approach was then applied to enantioselective synthesis of (–)-methyl dihydropalustramate. The key three-component sequential reaction smoothly proceeded to yield the product **102**, which was converted to (–)-methyl dihydropalustramate via oxazolinone **103** [61].

## 3.4.3.2 [4 + 2] Acylnitroso Cycloaddition

The formation of bicyclic- or tricyclic-nitrogen heterocycles has been reported by using [4 + 2] or formal [3 + 3] cycloaddition reaction as the key step.

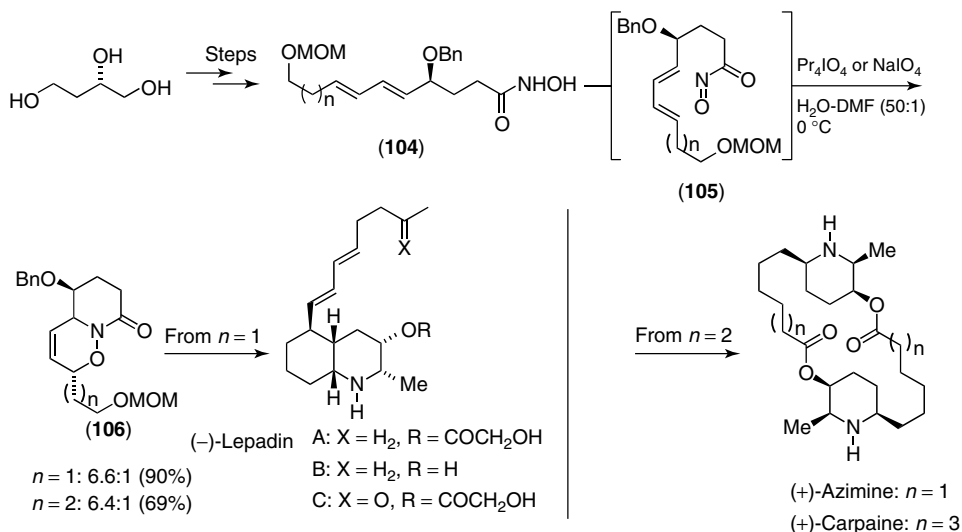
Kibayashi and Aoyagi studied the stereocontrolled intramolecular acylnitroso-Diels–Alder reaction to yield the bicyclic oxazino lactam. Oxidation of hydroxamic acid **104** with  $\text{Pr}_4\text{NIO}_4$  in aqueous media (water–DMF = 50:1) yielded the



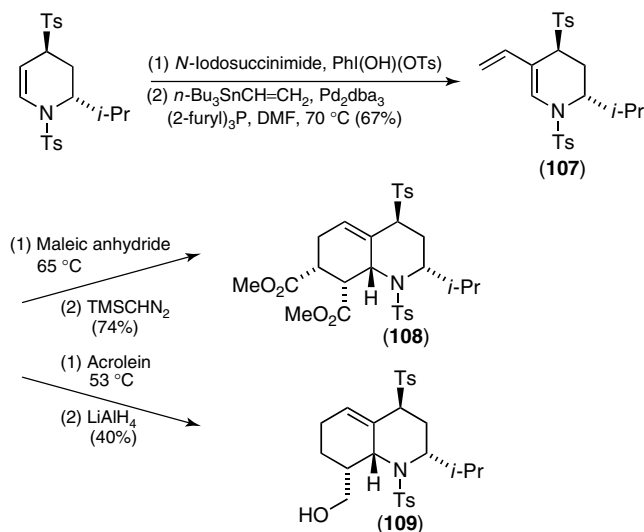
Scheme 3.38

cycloadduct **106** selectively (6.6:1) via acylnitroso compound **105**. Elaboration of **106** (stereoselective introduction of methyl substituent, construction of decahydroquinoline skeleton, and installation of the dienyl side chain) yielded the marine alkaloids (-)-lepadins A, B, and C [62, 63]. According to this method, the macrocyclic dilactones containing a 2,3,6-trisubstituted piperidine of (+)-azimine and (+)-carpaine have also been synthesized (Scheme 3.39) [64].

The Diels–Alder reaction of chiral 1,4-bis(arylsulfonyl)-1,2,3,4-tetrahydropyridine to yield the octahydroquinoline ring systems was achieved by Craig. Thus, the cycloaddition reaction of **107** with maleic anhydride or acrolein yielded the cycloadduct **108** or **109**, respectively. Formation of **108** or **109** indicated preferred endo approach of the dienophile toward the  $\alpha$ -face of **107** (Scheme 3.40) [65].



Scheme 3.39



Scheme 3.40

### 3.4.3.3 [3 + 2] Cycloaddition

The [3 + 2] 1,3-dipolar cycloaddition reaction of nitron is also an efficient methodology for the construction of chiral piperidine building blocks. Indeed, in this methodology, the cycloaddition allowed the formation of the C2–C3 bond of the piperidine ring along with the formation of the five-membered oxazolidine ring.

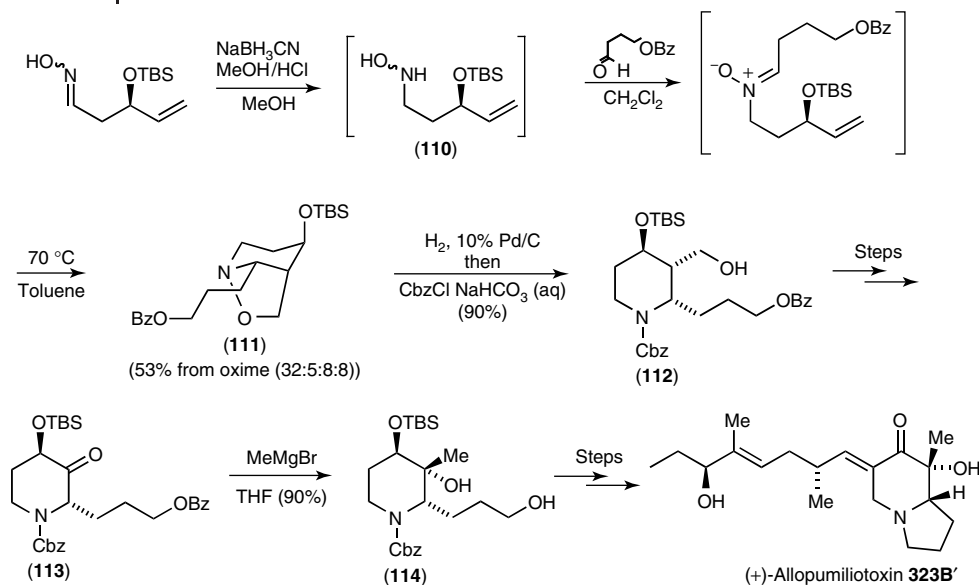
Poison-frog alkaloid (+)-allopumiliotoxin **323B** has been synthesized by Holmes employing the intramolecular [3 + 2]-cycloaddition reaction of *Z*-*N*-alkenylnitron to yield the precursor of 2,3,4-trisubstituted piperidine (Scheme 3.41). The key cycloaddition of **110** was conducted by heating at  $70^\circ\text{C}$  in toluene to yield four isoxazolidine cycloadduct (32:5:8:8). The major isomer **111** was converted to 2,3,4-trisubstituted piperidine **112**, which was transformed into the ketone **113**. The stereoselective addition of Grignard reagent to **113** was performed to yield the desired diol **114** as the sole product. The selectivity on this addition reaction was explained by  $\text{A}^{1,3}$ -strain and Cieplak hypothesis (Figure 3.3). The diol **114** was converted to (+)-allopumiliotoxin **323B** by the construction of the *exo*-olefin side chain [66].

### 3.4.4

#### Ring Transformation Methods

The construction of the piperidine ring can result from ring transformation and particularly from ring enlargement. The ring enlargement of five-membered ring systems such as pyrrolidine, lactone, or  $\gamma$ -lactam is also an effective method for the construction of six-membered nitrogen heterocycles. According to these





Scheme 3.41

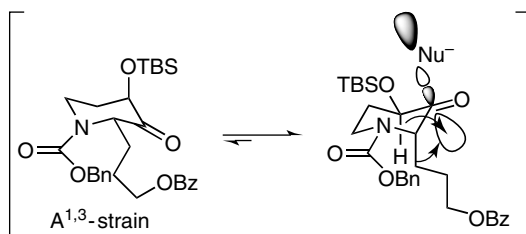


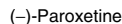
Fig. 3.3 Preferred conformer on Grignard-addition to 113.

enlargement methodologies, functionalized piperidine or 2-piperidone chiral building blocks are elaborated in highly stereoselective manner.

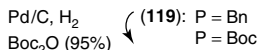
#### 3.4.4.1 Ring Enlargement of Pyrrolidines to Substituted Piperidines

A powerful method for the construction of piperidines is the ring transformation of prolinol derivatives. Cossy and Pardo described the ring expansion reaction of derivative 115, derived from L-pyrogutamic acid, by treatment with MsCl followed by Et<sub>3</sub>N to yield the 3,4,5-trisubstituted piperidine 116, which was used for asymmetric formal synthesis of (–)-paroxetine (Scheme 3.42) [67].

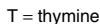
The asymmetric synthesis of *cis*-2,3-disubstituted 3-piperidinol 120, which is the useful intermediate for the synthesis of medicinally important neurokinin-1 receptor antagonists, has been reported by Lee [68] following a similar strategy. Thus, treatment of the prolinol derivative 118, prepared by the Jacobsen's asymmetric epoxidation of olefin 117 as the key step, with MsCl followed by *n*-Bu<sub>4</sub>NOAc



Scheme 3.42



**Scheme 3.43**



Scheme 3.44

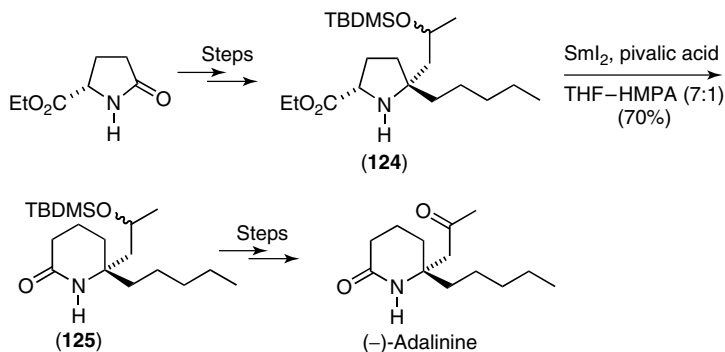
yielded **119** with high enantiomeric purity. This piperidine was also converted to 3-piperidone **121** by Moffat oxidation with no racemization (Scheme 3.43).

In the synthesis of chiral piperidine peptide nucleic acid (PNA), the ring enlargement of prolinol **122** yielded the key intermediate *trans*-3,5-disubstituted piperidine **123** (Scheme 3.44) [69].

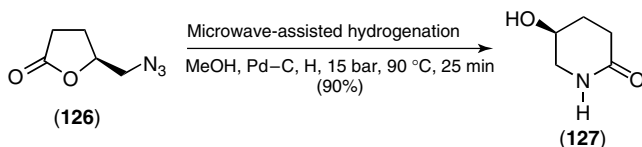
An original ring enlargement reaction of functionalized pyrrolidine **124** to piperidone **125** was proposed by Honda through a unique samarium-promoted C–N bond cleavage of **124** and simultaneous cyclization of the resulting amino ester to yield **125** (Scheme 3.45). The presence of pivalic acid as a proton source is essential in this transformation, and enantiospecific total synthesis of (–)-adalinine was also achieved. [70].

#### 3.4.4.2 Ring Transformation of Lactones to 2-Piperidones

The lactones bearing a nitrogen functionality such as an amino or azide group on the  $\gamma$ -substituent are suitable substrates for this transformation.



Scheme 3.45

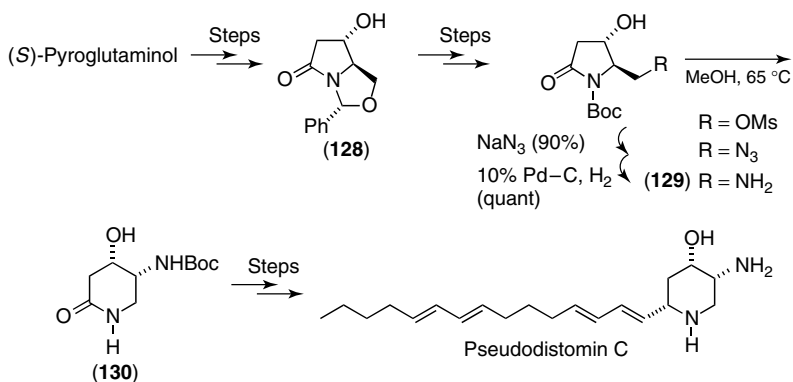


Scheme 3.46

Holzgrabe described the microwave-enhanced hydrogenation of azide-lactone **126** at the medium pressure to yield the 2-piperidone **127** in only 25 min with good yield (Scheme 3.46) [71].

#### 3.4.4.3 Ring Enlargement of $\gamma$ -Lactam to 2-Piperidones

Langlois described the synthesis of *cis*-4,5-disubstituted 2-piperidone **130** as a key intermediate for pseudodistomin C synthesis by ring expansion of aminomethyl-substituted  $\gamma$ -lactam **129** (Scheme 3.47). Thus, treatment of **129**, derived from (*S*)-pyroglutaminol via secondary alcohol **128**, in methanol at 65 °C for 24 h yielded transamidation product **130** with good yield, which was transformed into the marine alkaloid of pseudodistomin C [72].



Scheme 3.47

## 3.4.5

## Substitution of Already Formed Heterocycle

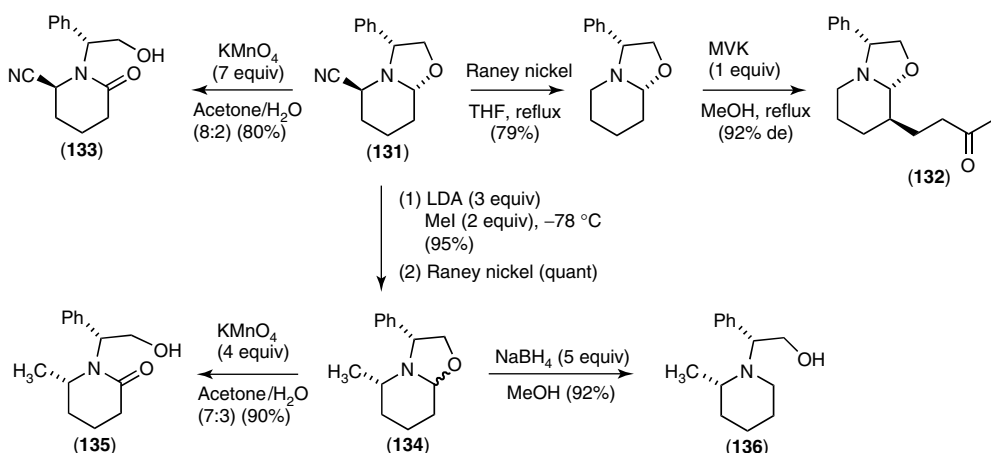
One strategy used in the asymmetric synthesis of piperidine was the preparation of a chiral and versatile building block that possesses the six-membered ring and can be further diversely substituted. This building block should be easily prepared with high yield and selectivity offering large possibilities of substitution. The substitutions should be stereocontrolled. The use of chiral auxiliaries is still the main strategy used, although some reactions using asymmetric catalysts were also reported.

## 3.4.5.1 Phenylglycinol-Derived Oxazolidine

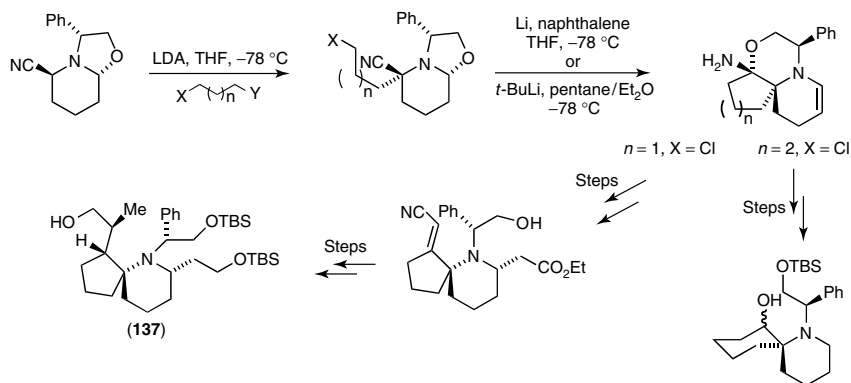
Enantiomerically pure phenylglycinol is frequently used for the induction of the chiral center on piperidine ring system. Involved in an oxazolidine ring, it allowed various diastereomerically controlled reactions that were exploited by several research groups in the preparation of piperidine derivatives.

Husson reported the reductive decyanation of the 3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-carbonitrile building block **86**, the key element of his elegant CN(*R,S*) strategy, with Raney nickel and its further application to other derivatives. This new piperidine scaffolds serve as stable 2-piperidine (enamine) equivalent in the rapid and efficient construction of 3-substituted piperidines **132** [73]. On the other hand, regioselective oxidative transformations of the *N*-(cyanomethyl)-oxazolidine system with potassium permanganate leading to enantiopure lactams have also been reported. Oxidation of **131** yielded the lactam **133**, which is a very versatile chiral building block for the synthesis of several alkaloids. This methodology can be applied to the conversion of **134** to chiral lactam **135** and piperidine **136**, as shown in Scheme 3.48 [74].

A unique approach to the synthesis of chiral nonracemic substituted [5,6]- and [6,6]-spiropiperidines was also described by the use of the CN(*R,S*) method



Scheme 3.48



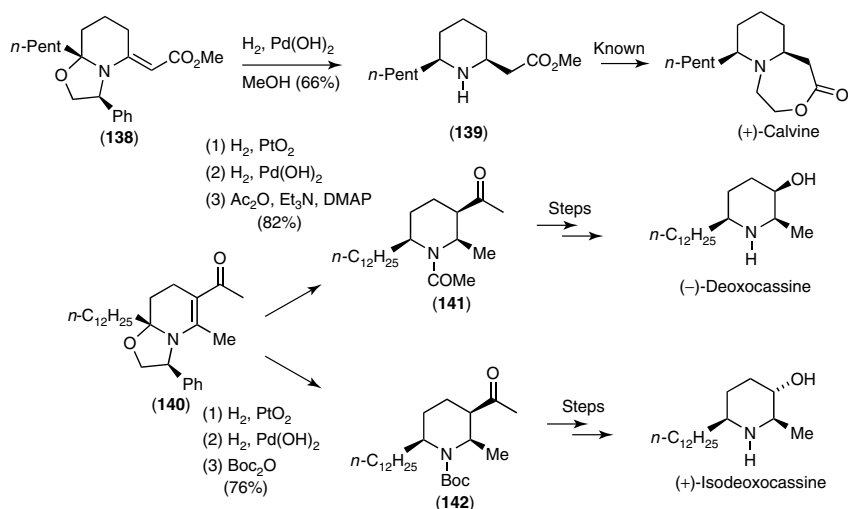
Scheme 3.49

(Scheme 3.49) [75]. Owing to the valuable application of this methodology to natural product synthesis, the advanced intermediate **137** in pinnaic acid series was achieved [76].

Lhommet developed the synthesis of chiral bicyclic  $\beta$ -enaminoester **138** by condensation of (*S*)-phenylglycinol on oxo alkynoate. The diastereoselective reduction of **138** was performed by hydrogenation of  $\text{Pd}(\text{OH})_2$  to yield the 2,6-*cis*-disubstituted piperidine **139** with an excellent enantioselectivity (>98%), which was a key intermediate previously reported in the total synthesis of (+)-calvine [77]. The construction of chiral bicyclic  $\beta$ -enaminoketone **140** by the same condensation procedure using the triketone instead of oxo alkynoate was also reported. The bicyclic  $\beta$ -enaminoketone **140** was converted to 2,3,6-trisubstituted piperidine **141** by hydrogenation of  $\text{PtO}_2$  followed by hydrogenolysis of  $\text{Pd}(\text{OH})_2$  in highly stereoselective manner. The piperidine **141** was transformed into (–)-deoxocassine. On the other hand, the trisubstituted piperidine **142**, derived from **140**, was converted to (+)-isodeoxocassine via the epimerization on the 3-position (Scheme 3.50) [78].

Substitution reactions on the already formed heterocycle using the acyliminium ion strategy have been widely studied, and constitute an effective method for the construction of chiral piperidine ring.

Such strategy was the basis of Amat and Bosch enantioselective syntheses of piperidine alkaloids. Mono-substituted piperidine (*R*)-coniine, 2,6-*cis*-disubstituted piperidine alkaloid (2*R*,6*S*)-dihydropinidine, 2,6-*trans*-substituted piperidine alkaloids (2*R*, 6*R*)-lupetidine and (2*R*,6*R*)-solenopsin A, and indolizidine alkaloids (5*R*,8*aR*)-indolizidine **167B** and (3*R*,5*S*,8*aS*)-monomorine I were prepared starting from both enantiomers of a common Meyers' type lactam, (3*R*,8*aS*)-5-oxo-3-phenyl-2,3,6,7,8,8*a*-hexahydro-5*H*-oxazolo[3,2-*a*]pyridine. Addition of allyl moiety on **143** in the presence of  $\text{TiCl}_4$  yielded the product in a diastereoselective manner. The selectivity observed here was rationalized by the nucleophilic attack upon the less hindered *Re* face on the iminium ion, whose conformation is restricted by the chelation, as shown in Figure 3.4. Thus, the mono-substituted piperidine alkaloid



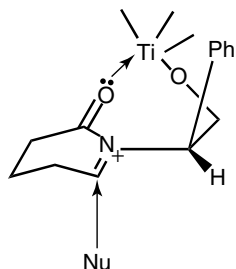
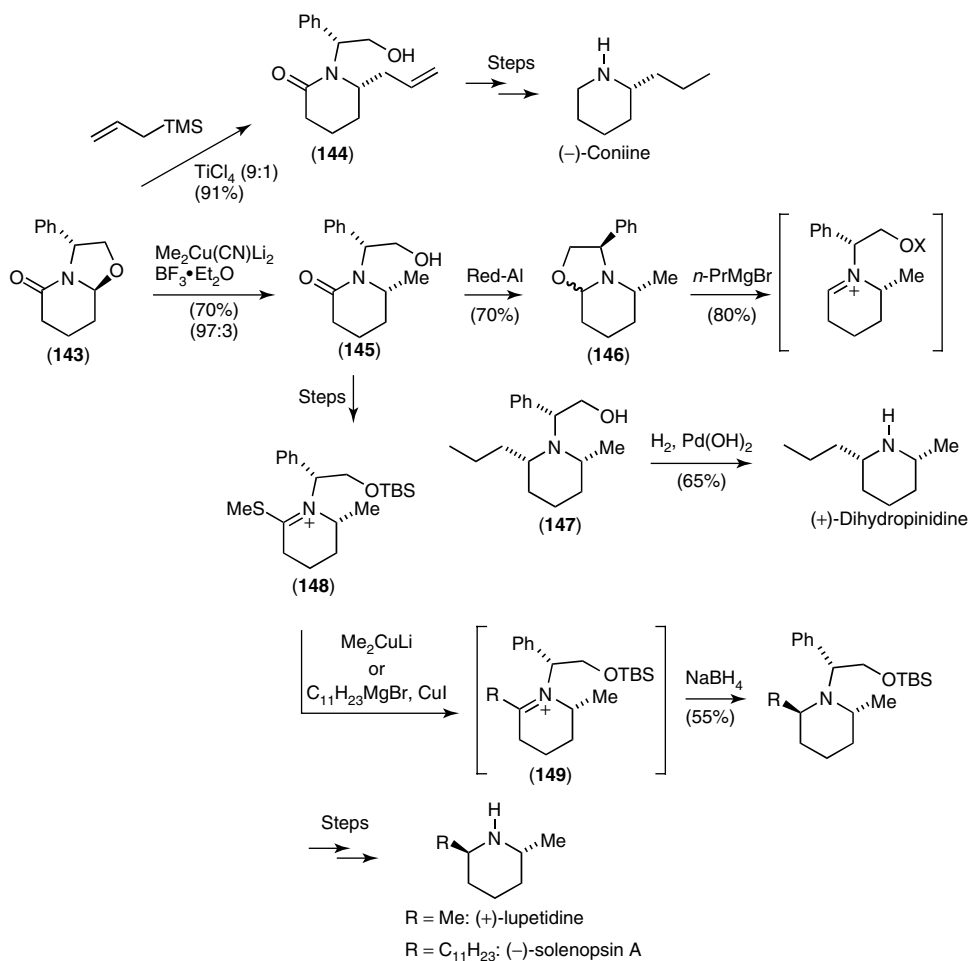
Scheme 3.50

of (–)-coniine was synthesized from **144** in several steps. Similarly, the addition of higher-order cyanocuprate to **143** in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  yielded the adduct **145** in highly diastereoselective manner. Partial reduction of **145** with Red-Al yielded the masked iminium ion **146**, which was made to react with Grignard reagent to yield **147** as the only isolated product with good yield. This stereoselectivity was explained by stereoelectronic effects. Further reactions on **147** yielded 2,6-*cis*-disubstituted piperidine alkaloid of (–)-dihydropinidine. Likewise, the syntheses of (–)-indolizidine **167B** and (+)-monomorine I have also been achieved. On the other hand, the iminium reduction of **149** ( $\text{R} = \text{Me}$  or  $\text{C}_{11}\text{H}_{23}$ ) derived from **148** with  $\text{NaBH}_4$  yielded the 2,6-*trans*-disubstituted piperidines, which was converted to lupetidine and solenopsin A, respectively (Scheme 3.51) [79].

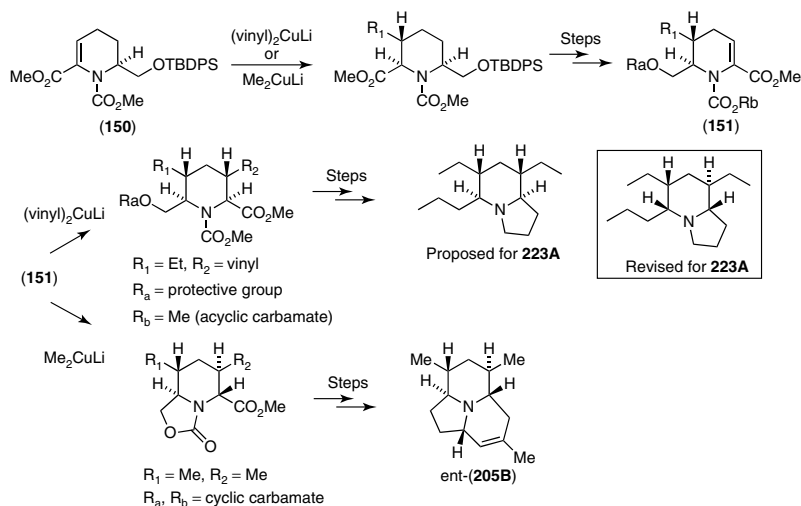
This methodology was extended to the synthesis of 3,5-*cis*- and *trans*-disubstituted, 2,5-disubstituted, and 2,3,5-trisubstituted enantiopure piperidines, and the indole alkaloids 20*R*- and 20*S*-dihydrocleavamine [80].

#### 3.4.5.2 Asymmetric Michael Addition

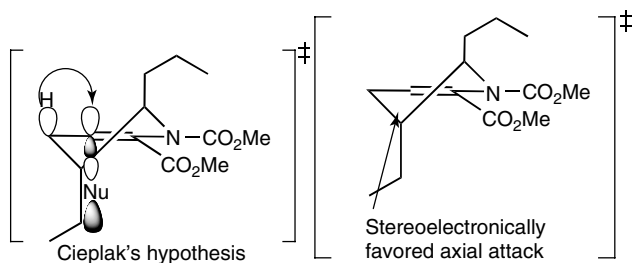
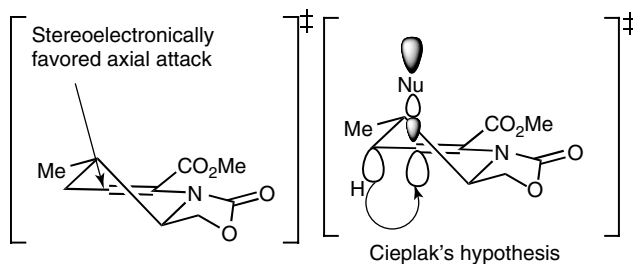
Toyooka disclosed the stereodivergent construction of 2,3,5,6-tetrasubstituted piperidine ring system by sequential use of key Michael-type conjugate addition reaction of the enaminoesters **150** and **151** (Scheme 3.52). Thus, the first enantioselective synthesis of poison-frog alkaloid **223A** and the structural revision were achieved [81]. On the other hand, the first enantioselective synthesis of unique tricyclic poison-frog alkaloid ent-**205B** [82, 83] was also achieved. The observed remarkable stereoselectivity of key conjugate addition reaction can be rationalized by the stereoelectronic effect and is also consistent with Cieplak's hypothesis, as shown in Figures 3.5 and 3.6.

Fig. 3.4 Diastereoselective addition to **143** controlled by chelation.

Scheme 3.51



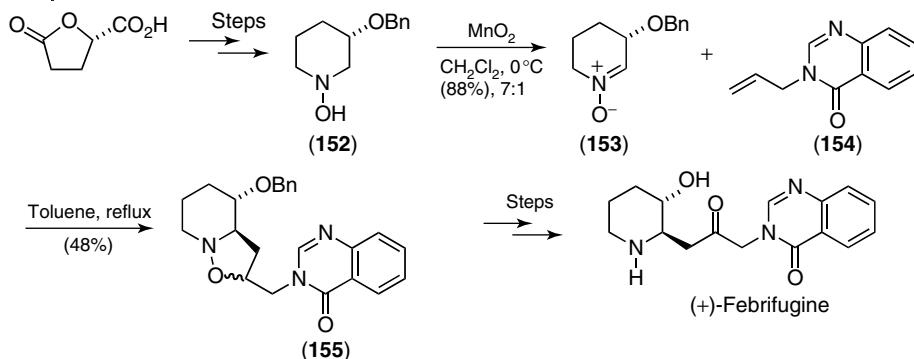
Scheme 3.52

Fig. 3.5 Stereochemical course of Michael-type addition to **151** (acyclic carbamate).Fig. 3.6 Stereochemical course of Michael-type addition to **151** (cyclic carbamate).

### 3.4.5.3 Nitronc Cycloaddition

The 1,3-dipolar cycloaddition reaction of chiral six-membered ring of nitronc **153** was the key step in a convergent enantioselective synthesis of (+)-febrifugine.



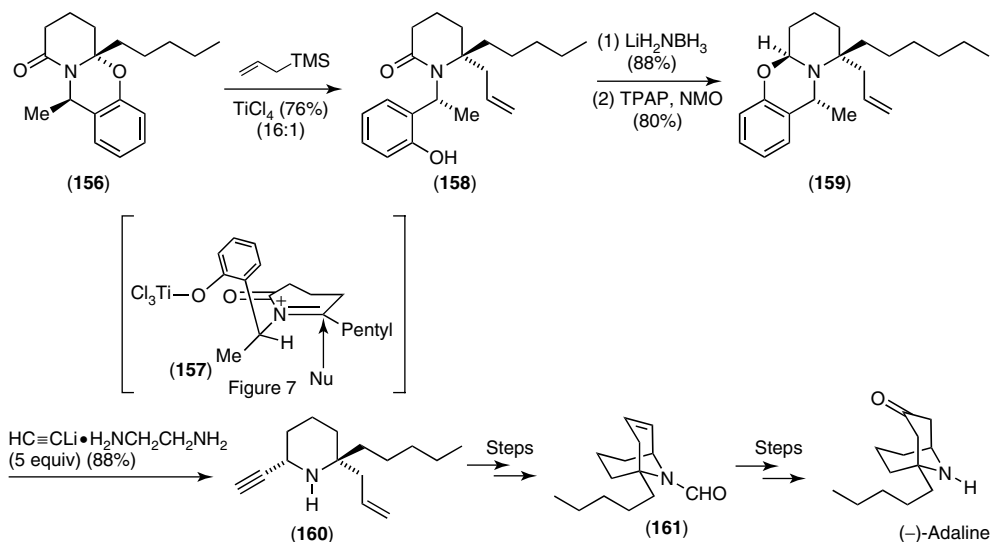


Scheme 3.53

Thus, the oxidation of piperidine **152**, which was derived from L-glutamic acid, with  $\text{MnO}_2$  yielded a 7:1 mixture of separable regioisomeric nitorones. Key 1,3-dipolar cycloaddition reaction of **153** with quinazolinone **154** yielded the adduct **155** as the major isomer. This isoxazolidine was converted to (+)-febrifugine in several steps, as shown in Scheme 3.53 [84].

#### 3.4.5.4 Iminium Strategies

Yamazaki and Kibayashi described the construction of the quaternary center at the  $\alpha$ -position of the piperidine ring using the acyliminium addition reaction on similar tricyclic *N*-acyl-*N*,*O*-acetal **156**. This method was applied to the asymmetric synthesis of (–)-adaline. Lewis acid promotes C–O bond cleavage to form the *N*-acyliminium ion, which preferably conforms with the hydrogen atom in the



Scheme 3.54

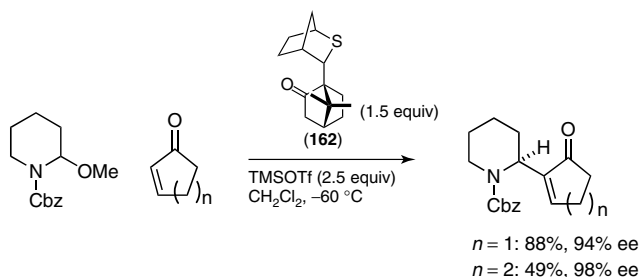
inside position to minimize the 1,3-allylic strain. Subsequent nucleophilic addition to **157** is expected to occur from the less hindered bottom face leading to the *R* configuration in the piperidone to give **158** (Figure 3.7). Reduction of **158**, and then tetrapropyl-ammonium perruthenate (TPAP) oxidation of the resulting alcohol yielded **159**. Upon treatment of **159** with lithium acetylide ethylenediamine complex, the nucleophilic alkynylation proceeded with complete inversion of configuration at the reaction center with concomitant removal of the 1-(2-hydroxyphenyl)ethyl function via C–N bond cleavage to yield **160** as the sole diastereomer. Further elaborations on **160** via **161** yielded the (–)-adaline (Scheme 3.54) [85].

The asymmetric Morita–Baylis–Hillman type reaction of six-membered *N*, *O*-acetal with cyclic enones was reported by Aggarwal. In the presence of chiral sulfide **162** derived from camphor sulfonic acid and TMSOTf, high enantioselectivity was achieved (Scheme 3.55). In this reaction, the use of piperidine-based *N*, *O*-acetal yielded the adducts with improved enantioselectivity values compared to the pyrrolidine series.

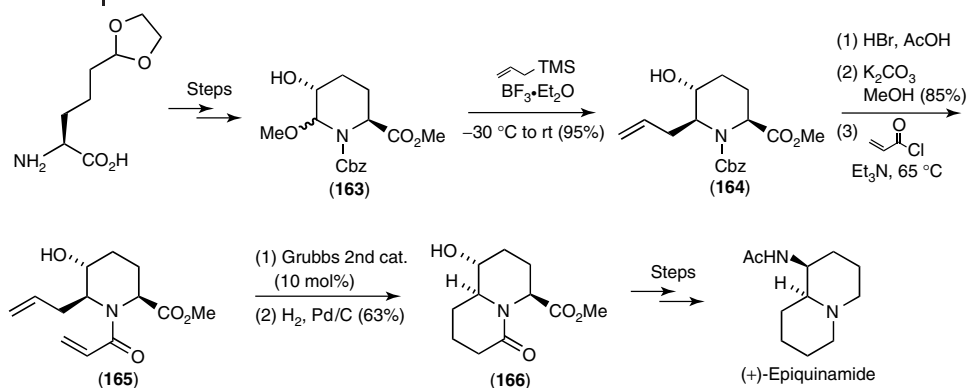
When the acyclic enone methyl vinyl ketone (MVK) was employed, the enantioselectivity value of the corresponding adduct was very low [86].

Blaauw reported the total synthesis of (+)-epiquinamide by using a highly diastereoselective *N*-acyliminium ion allylation, and RCM to yield a quinolinone skeleton. The *N*-acyliminium allylation of **163** yielded the 2,3,6-trisubstituted piperidine **164**, which was converted to acrylamide **165**. The RCM reaction of **165** using Grubbs 2nd catalyst yielded the quinolinone **166**, which was transformed into (+)-epiquinamide in several steps, as shown in Scheme 3.56 [87].

In the following example, the synthesis of new six-membered multifunctional chiral building block **167** was obtained through the ring transformation of an optically active butenolide (as already illustrated in Section 3.4.4). Imide **167** is a very versatile chiral building block for the synthesis of natural alkaloids such as epiquinamide [88], homopumiliotoxin **223G** [88], deoxocassine [89], and biologically important molecules such as L-733,060 [90], L-733,061 [89], and CP-99,994 [90]. The key feature of Huang's approach is regio- and diastereoselective installation of the nucleophile on the 2-position of **167**. On treatment of piperidinol, derived from regioselective reduction of **167** with NaBH<sub>4</sub> and then with BF<sub>3</sub>•Et<sub>2</sub>O, the phenyl

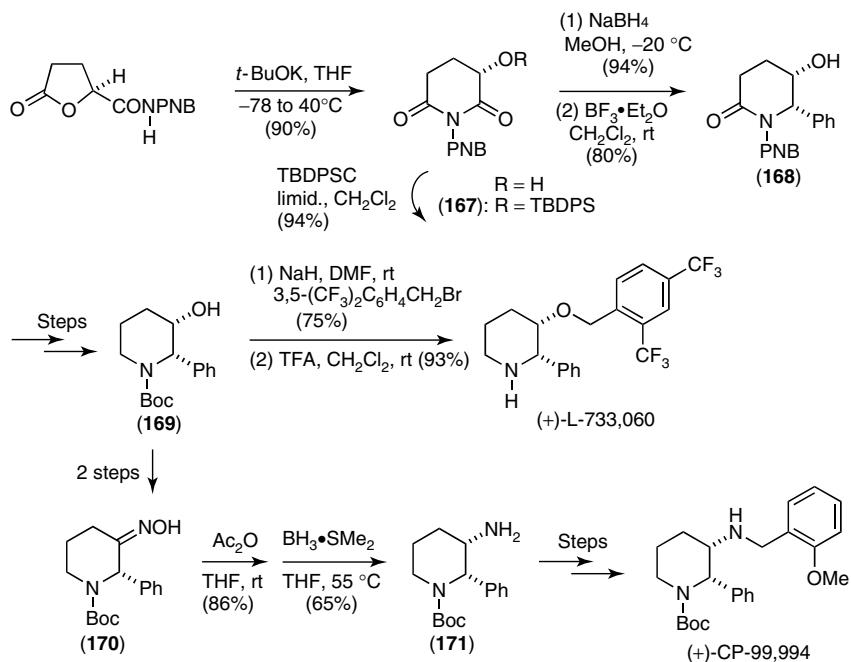


Scheme 3.55



Scheme 3.56

migration from the *tert*-butyldiphenylsilyl (TBDPS) protective group smoothly proceeded to yield **168** in 80% isolated yield with high *cis* (>95%) selectivity. Reduction of lactam moiety and deprotection of *para*-methoxy-benzyl (PMB)-group followed by protection with (Boc) $_2$ O yielded **169**. Further two-step treatment of **169** yielded (+)-L-733,060. On the other hand, the Boc-derivative **169** was transformed into the amino-derivative **171** via the reduction of the corresponding oxime **170**. Further elaboration yielded (+)-CP-99,994 (Scheme 3.57).



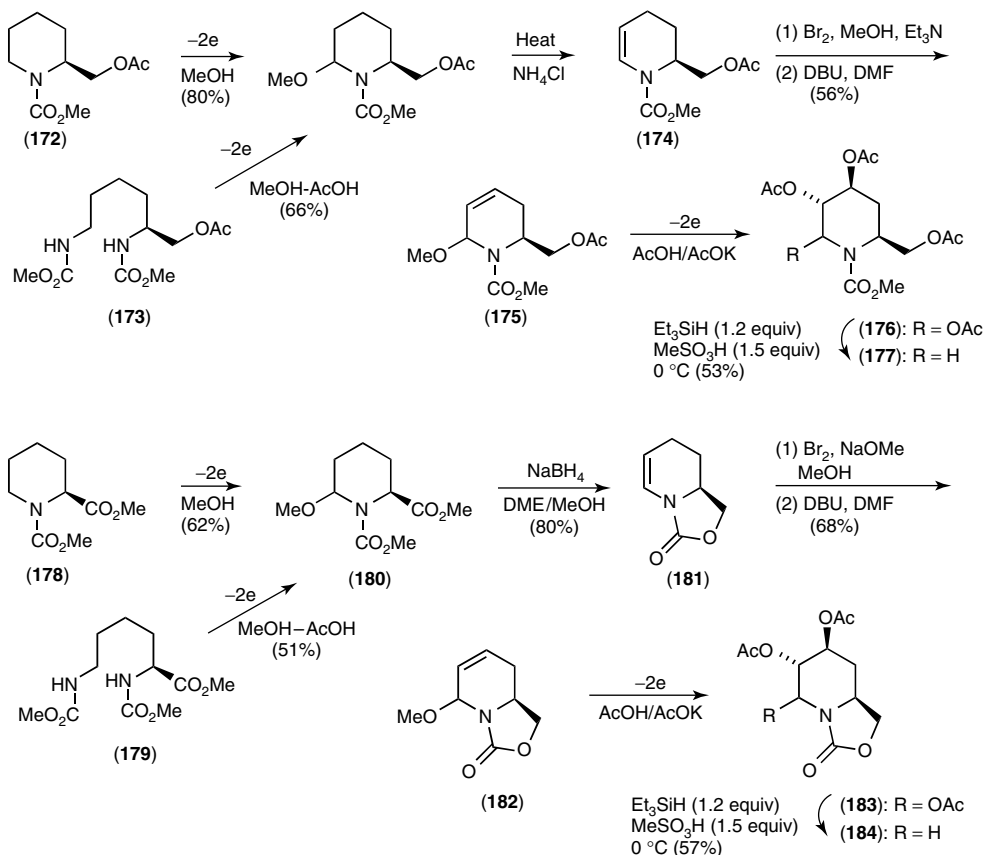
Scheme 3.57

## 3.4.5.5 Oxidative Methods

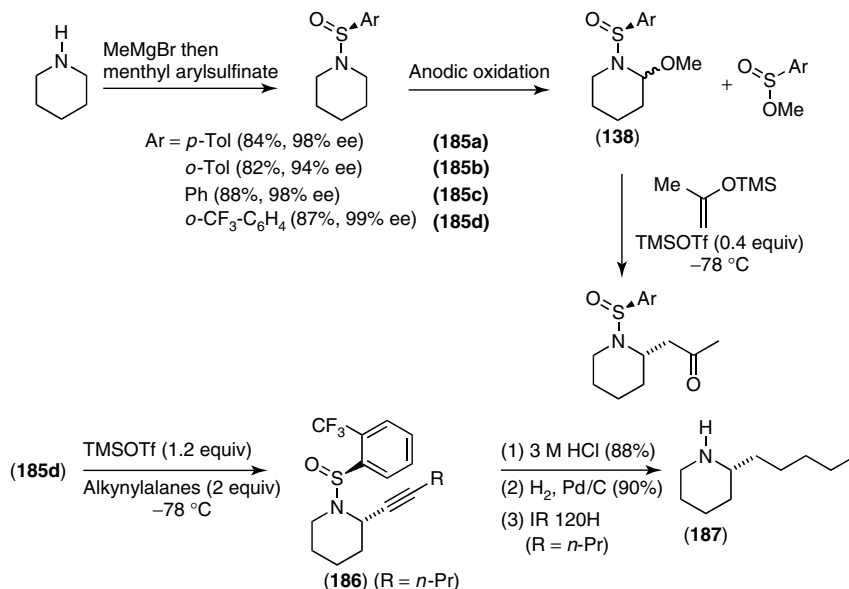
Oxidative methods, and particularly electrochemical process, proved to be valuable in the asymmetric synthesis of nitrogen compounds and piperidine derivatives. For example, the stereoselective synthesis of azasugars was obtained by Matsumura through the electrochemical oxidation of chiral piperidine derivatives. The enaminoester **100** was synthesized by anodic oxidation of **172** or **173** in 80% and 66% yield, respectively. After conversion of **174** to **175**, the latter was subjected again to electrochemical oxidation to yield **176**. The reduction of **176** with  $\text{Et}_3\text{SiH}$  yielded **177** as the major isomer. On the other hand, electrochemical oxidation of **178** or **179** yielded **180** in 62% and 51% yield, respectively, which was then converted to **181**. The electrochemical oxidation of **182** yielded **183**, whose  $\alpha$ -acetoxy moiety was reduced with  $\text{Et}_3\text{SiH}$  to give **184** (Scheme 3.58) [91].

The sulfinyliminium salt instead of acyliminium ion is also effective for the enantioselective nucleophilic substitution on the six-membered ring system.

Royer reported the asymmetric synthesis of mono-substituted piperidine using the nucleophilic addition to the chiral *N*-sulfinyliminium salts. The first example



Scheme 3.58



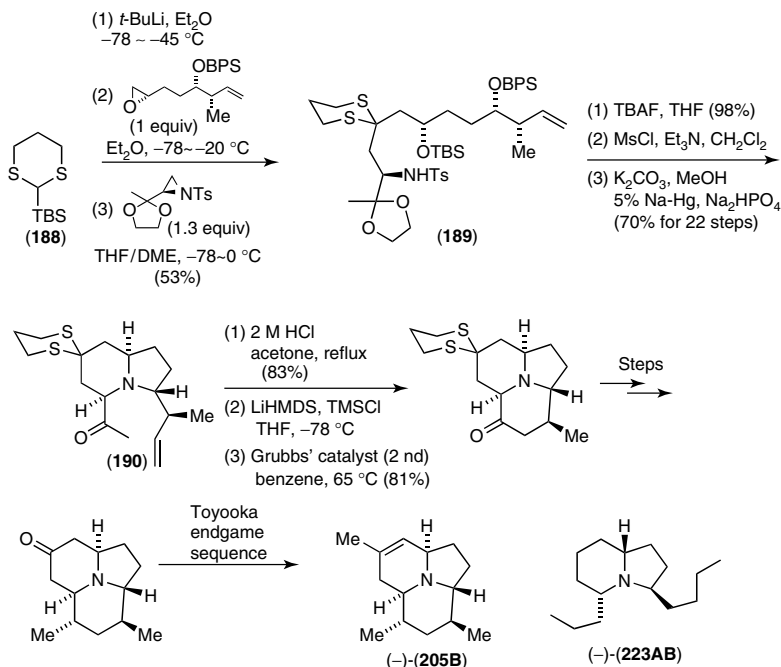
Scheme 3.59

was the anodic oxidation of chiral sulfinylpiperidines, which was prepared from piperidine and menthyl arylsulfonates in high yields (82–88%) and enantioselectivity (94–99% ee). The anodic oxidation of **185** yielded α-methoxylated sulfinylamines along with the N–S bond cleavage products (~15%). Diastereoselective addition of trimethylsilylpropene to the corresponding iminium salts, derived from **185 d** with TMSOTf, proceeded to yield the adducts in acceptable diastereoselectivities (64–84% de). α-Alkynylation, as a further application of the chiral sulfinyliminium salt to the synthesis of mono-substituted piperidine, was also investigated. In this reaction, *o*-trifluoromethylsulfinylpiperidine showed best result, and the α-alkynylated products were obtained with high diastereoselectivities (92–97% de). The absolute configuration of the adduct was assigned by conversion of **186** to known **187** (Scheme 3.59) [92].

### 3.5

#### Fused Tri- or Bicyclic System with Bridgehead Nitrogen

Several syntheses of bicyclic systems with bridgehead nitrogen have already been described in the above sections as an illustration of synthetic methods used in the asymmetric synthesis of piperidines (see Sections 3.2, 3.3.4, 3.3.5, Nitrogen α-Carbanion, Iminium Addition, 3.3.2.3, 3.4.5.1, and 3.4.5.4). Some examples reported in the present section could also be considered as piperidines synthesis, though, in general, they are more specific methods directed toward the preparation of polycyclic systems.

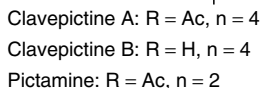


Scheme 3.60

A stereocontrolled total synthesis of natural enantiomer of poison-frog alkaloid (-)-**205B** has been achieved employing a one-pot construction of the embedded indolizidine skeleton as a key step. Thus, the dithiane three-component linchpin coupling reaction of **140** with aziridine and epoxide yielded the desired compound **141**. The one-pot construction of the indolizidine ring system was achieved by the removal of the silyl groups, bismesylation of the resulting diol, and treatment of the bismesylate with potassium carbonate in  $\text{MeOH}$ , followed by the addition of sodium amalgam to yield the indolizidine **142** (69% yield). This indolizidine was transformed into the natural enantiomer of (-)-**205B**. The indolizidine (-)-**223AB** was also synthesized by this convergent strategy (Scheme 3.60) [93, 94].

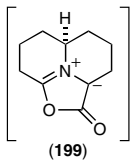
A highly diastereoselective quinolizidine ring closure reaction allowed Ma's group to achieve the total synthesis of marine alkaloids clavipictines A and B, and pictamine. Thus, the reaction of  $\beta$ -keto sulfone with chiral amine yielded the enamine sulfone **191**, which was then converted to alcohol **192** by iminium reduction and to precursor for the key intramolecular conjugate addition reaction. The key cyclization was performed by treatment of **193** with  $\text{AlCl}_3$  followed by exposure of the liberated amine to aqueous  $\text{NaHCO}_3$  to yield **195** via the most stable conformer **194**. After installation of the dienyl side chain by Julia coupling reaction, the total syntheses of clavipictines A and B, and pictamine were completed, as shown in Scheme 3.61 [95].

Angle's group reported the general synthesis of pyrroloquinolizidines using münchnone 1,3-dipolar cycloaddition as the key step. The strategy was applied to the

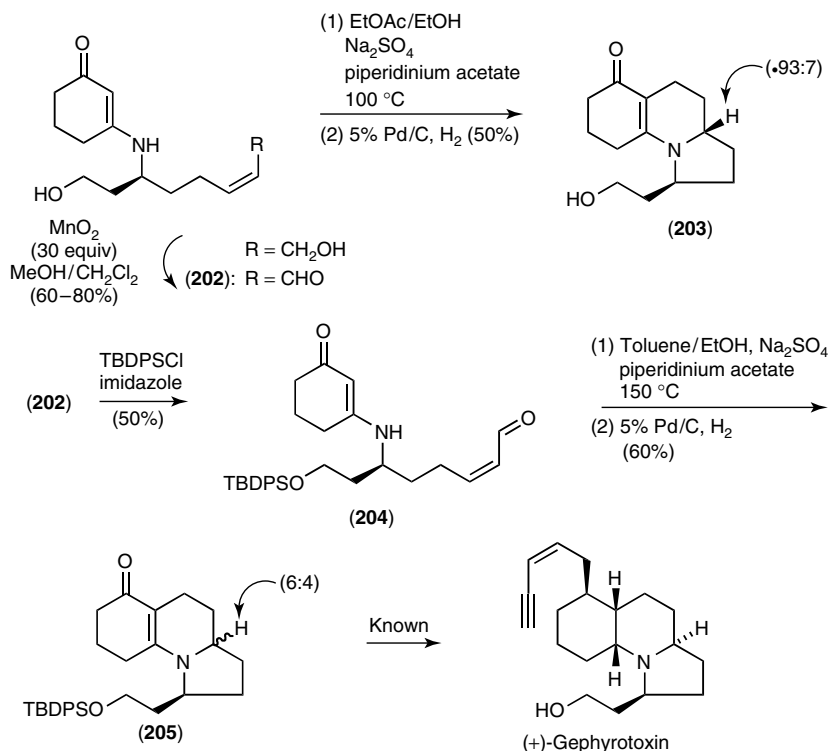


Scheme 3.61

synthesis of unnatural homolog of the ant-alkaloid mymicarin 215B. The chiral bicyclic lactam **197**, prepared from **196**, was subjected to 1,3-dipolar cycloaddition reaction with disubstituted alkyne **198** to yield the adduct **200**, which was then transformed into **201**, a homolog of mymicarin 215B. This is the first example of the



**Scheme 3.62**



Scheme 3.63

1,3-dipolar cycloaddition using the tricyclic münchnone such as **199** (Scheme 3.62) [96].

A novel and highly stereoselective intramolecular formal [3 + 3] cycloaddition reaction of vinylogous amides tethered with  $\alpha,\beta$ -unsaturated aldehydes allowed straightforward access to indolizidine skeleton. This methodology was extended to efficient formal synthesis of gephyrotoxin. Thus, the cycloaddition of **202** yielded the tricyclic compound **203** with high stereoselectivity. This ring system was key intermediate for the synthesis of gephyrotoxin; however, the stereochemistry of the newly formed position was opposite for gephyrotoxin synthesis. On the other hand, the cycloaddition of **204** yielded the desired cycloadduct **205**, which is the key intermediate of the Kishi's gephyrotoxin synthesis, although the stereoselectivity on the key cycloaddition reaction was low (Scheme 3.63) [97].

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## 4

## Asymmetric Synthesis of Seven- and More-Membered Ring Heterocycles

*Yves Troin and Marie-Eve Sinibaldi*

Seven-membered ring nitrogen heterocycles (azepines) together with more-membered substrates, in particular azocines (eight-membered azacycles) and sometimes azonines (nine-membered azacycles), are important classes of compounds occurring in a range of natural and synthetic products with interesting biological activities leading to application in pharmaceutical research [1a,b,c]. However, the generation of these medium-sized ring molecules, in particular of the eight or more-membered ring compounds, constitutes always a challenge in organic synthesis.

We summarize herein the different asymmetric methods described for the elaboration of these skeletons.

### 4.1

#### Substituted Azepines

##### 4.1.1

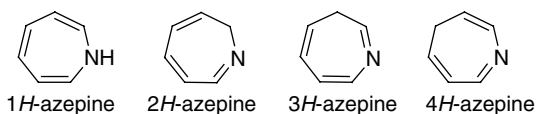
##### Generalities

The azepine (azacycloheptatriene system) exists in four tautomeric forms with the relative stability,  $3H > 1H > 2H > 4H$  (Scheme 4.1).

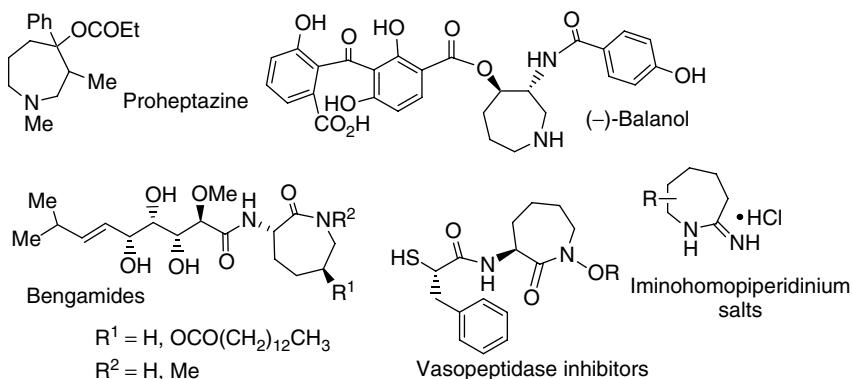
Dihydro- and tetrahydroazepines are the most common azepine substrates forming the pharmacophores of many biologically active compounds [1d].

For example, simple N-substituted hexahydroazepines are interesting substrates which are recognized as antitussives, mydriatics, antispasmodics and oral hypoglycemics, and, azepan-2-one ( $\epsilon$ -caprolactam) which has been industrially used in the production of perlon constitutes the cornerstone starting material in the preparation of more elaborated azepanes.

Moreover, variously substituted hexahydroazepines are compounds of particular interest. Thus, hexahydro-azepin-4-ol derivatives possess most often analgesic properties; for example, proheptazine is recognized to have twice the analgesic effect of morphine without addictive effects. Balanol, a bisubstituted hexahydro-azepine is an antineoplastic inhibitor of protein kinase C and plays an important role in cellular growth control, regulation and differentiation (Scheme 4.2) [1e].



Scheme 4.1 Azepine systems.



Scheme 4.2 Azepanes with biological activities.

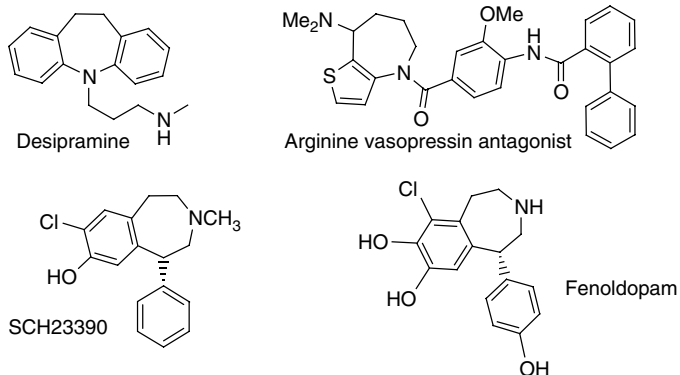
Imino-homopiperidinium salts are known to be selective inhibitors of inducible nitric oxide synthase and could be therefore considered as therapeutic agents in arthritis (Scheme 4.2) [1f].

Seven-membered lactams are also of considerable interest in drug discovery and pharmaceutical research. For example, the bengamides, a family of marine natural products differing only in their lactam moiety, show anthelmintic and antitumor activities [1g]. Hydroxamic acid-derived azepinones are depicted as vasopeptidase inhibitors having selective angiotensin-converting enzyme (ACE) and neutral endopeptidase (NEP) inhibition (Scheme 4.2) [1h].

Moreover, the aza-seven-membered ring could be also found fused with other rings leading to structures with various interesting properties.

In particular, benzazepines constitute a core scaffold of many active compounds including integrin antagonists [1i], selective 5HT<sub>2C</sub> receptors agonists [1j] or oxytocin (OT) receptors [1k]. Dihydrobenzoazepines are components of a series of psychopharmaceuticals such as desipramine [1l] (Scheme 4.3). Benzazepine-3-one and its derivatives have been used as adrenaline antagonists, inflammation inhibitors, drugs with cholesterol-lowering properties, or mediators in cellular adhesion events. Phenylbenzazepines possess selective dopamine D<sub>1</sub> agonist or antagonist properties, like SCH23390 or Fenoldopam (Scheme 4.3) [1m]. Recently, fused azepine like thieno[3,2-*b*] azepine derivatives which acted as arginine vasopressin antagonists were also synthesized (Scheme 4.3) [1n].

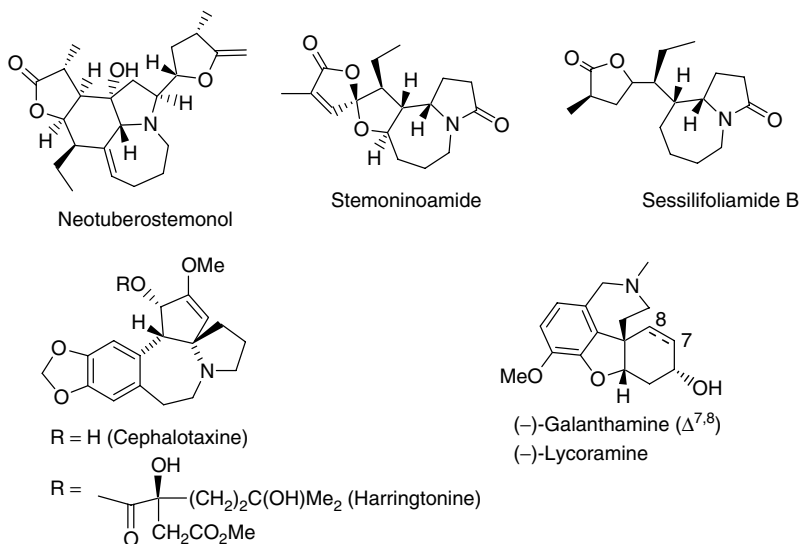
Many polycyclic complex alkaloids, including an azepine ring in their skeleton, also exhibited interesting properties and were therefore suitable targets for total synthesis.



**Scheme 4.3** Fused-azepine derivatives.

Among them, we found the *Stemona* alkaloids [1o] with a pyrrolo[1,2-a]azepine core like stemoninoamide, neotuberostemonine, and so on, the extracts of which have been used for years in China and Japan as human cough remedies and also as an antihelminthic in domestic animals. More recently, insecticidal properties also have been recognized (Scheme 4.4) [1p].

We can also mention the *Amaryllidaceae* family with the well-known alkaloid (–)-galanthamine possessing a seven-membered aza nucleus fused with a 2,3-dihydrobenzo[*b*]furan. This compound commercially available as Razadyne acts as a selective acetylcholinesterase inhibitor and is in clinical use for the symptomatic treatment of Alzheimer's disease [1q]. Lycoramine a member of galanthamine type alkaloid family has similar but albeit less potent activity (Scheme 4.4).



**Scheme 4.4** Polycyclic complex alkaloids with azepine ring.

Finally, but without being exhaustive, alkaloids from *Cephalotaxus* genus owning a spiro-fused benzazepine core are of considerable current interest, in particular the well-known naturally occurring ester derivative homoharringtonine (HHT) which exhibits antitumor activities [1r,s].

The different methods related to prepare the seven-membered heterocyclic ring of azepine derivatives are classified in four concepts: cyclization, cycloaddition reactions, ring transformation processes, or substitution of a preformed seven-membered ring.

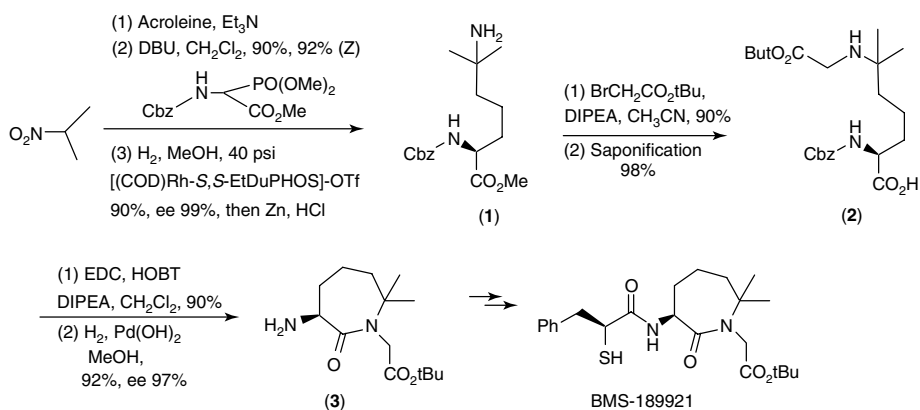
#### 4.1.2

#### Cyclization Methods

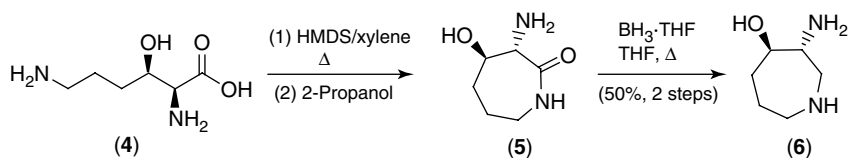
##### 4.1.2.1 Lactamization: C–N Bond Formation

The intramolecular reaction of an  $\omega$ -aminoester is the most current route to prepare azepanes but provided in most cases low yields of the desired seven-membered lactams. Activation of either the carboxyl or the amino function together with the use of coupling reagents (catecholborane, carbodiimide, (Benzotriazol-1-yloxy) tris(dimethylamino)phosphonium hexafluorophosphate (BOP), Diphenylphosphoryl azide (DPPA), etc.) allowed to increase the yield of the reaction [2].

Thus, an efficient asymmetric synthesis of the vasopeptidase inhibitor BMS-189921 was reported starting from **1**, prepared in four steps from 2-nitropropane using an enantioselective hydrogenation with (+)-1,2-bis((2*S*,5*S*)-2,5-diethylphospholano)-benzene (cyclooctadiene) thodium(1)trifluoromethanesulfonate([(COD)Rh-(*S,S*)-EtDuPHOS]OTf) followed by a Zn, HCl/MeOH reduction of the nitro group [3]. Alkylation and selective saponification of the methyl ester gave the azepine precursor **2** in 88% yield. Formation of the seven-membered ring was performed by lactamization of the amino acid using *N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC)/1-hydroxybenzotriazole (HOBT)/diisopropylethylamine (DIPEA) in dichloromethane providing the azepinone **3** in a 90% yield with less than 2% epimerization (Scheme 4.5).



**Scheme 4.5** Synthesis of BMS-189921 azepine ring.



**Scheme 4.6** Synthesis of azepine fragment of (–)-balanol.

The lactam ring cyclization process has been applied to prepare the azepine frameworks of other simple seven-membered lactams such as **6** or **10**, precursors of (–)-balanol [4] and bengamides, respectively [5].

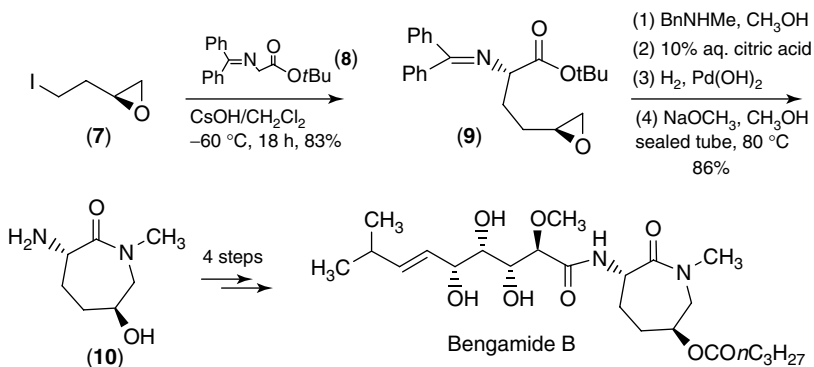
Thus diamine **4** obtained in 82% ee from 4-chloro-1-butanol *via* an asymmetric amino-hydroxylation step underwent a basic intramolecular cyclization affording the  $\epsilon$ -caprolactam **5** which could be further transformed by reduction into the expected azepine fragment of (–)-balanol **6** (50% in two steps, Scheme 4.6).

Similar methodology has been applied to the synthesis of bengamide B [5]. Idoepoxide **7**, prepared from (*D*)-aspartic acid was treated with the commercially available imine **8** to give the glycinate **9** in 83% yield as a single diastereomer. After ring opening of the epoxide with benzylmethylamine followed by imine hydrolysis of the amino-alcohol intermediate, the seven-membered ring closure was effected in a sealed tube in basic medium leading to **10** in 86% yield from **9** (Scheme 4.7).

Extension of the lactamization reaction allowed also the preparation of bicyclic 5,7-fused lactam. For example, condensation of (*S*)-valinol and 2'-formylbiphenyl-2-carboxylic acid **11**, available in two steps from diphenylhydrazide, provided under dehydrating conditions lactams **12** as a mixture of two epimers in 96% yield with a 75% de (Scheme 4.8) [6].

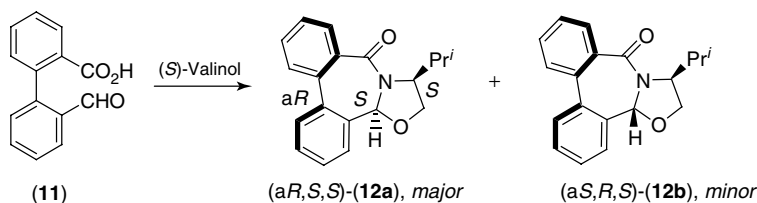
In a similar way, stereoselective formation of the 5,7-fused bicyclic lactam **16** has been realized under the classical dehydrating conditions developed by Meyers [7].

Keto-acid **15** ( $R = H$ ) obtained *via* the Suzuki cross-coupling reaction of commercially available boronic acid **13** with aryl halides **14** led, efficiently, to lactam **16** in the presence of (*R*)-phenylglycinol with good diastereoselectivity. Treating the

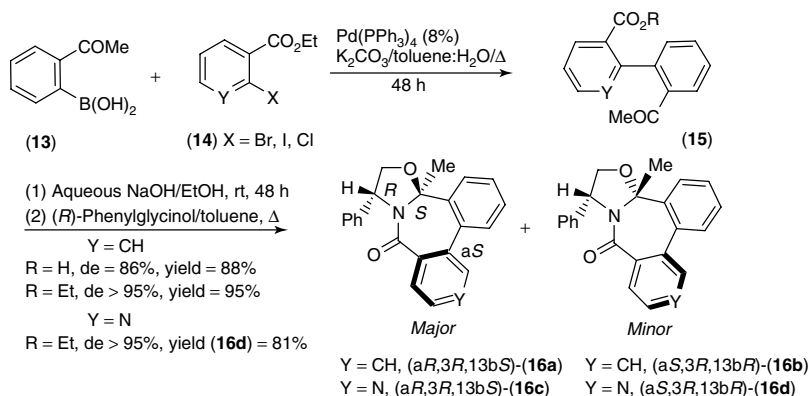


**Scheme 4.7** Synthesis of the seven-membered lactam ring of bengamide B.





**Scheme 4.8** Lactamization to bicyclic 5,7-fused lactam.



**Scheme 4.9** Use of phenylglycinol in the synthesis of bicyclic 5,7-fused lactam.

ester of **15** (R = Et) under the same conditions furnished the lactam **16b** as a single isomer in more than 90% yield (de > 95%).

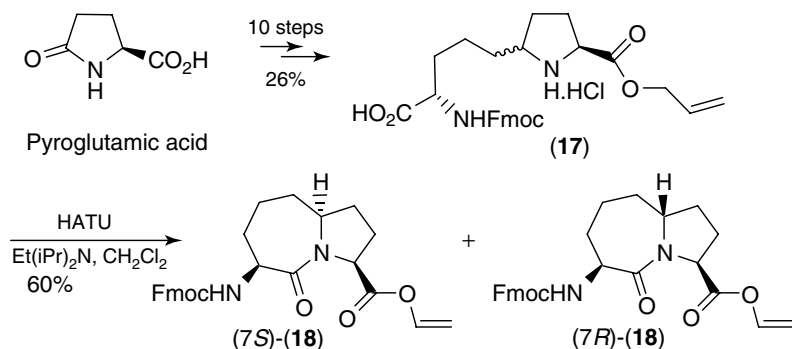
A successful application concerned the preparation of the lactams **16c,d** incorporating now a heterocyclic ring (Scheme 4.9) [8].

Pyrroloazepinone aminoacid (7*R*)-**18** or (7*S*)-**18** was prepared in 11 steps and 13% overall yield from pyrrolidine **17**, easily obtained from pyroglutamic acid. The seven-membered ring cyclization was realized using, either *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexa-fluorophosphate (HATU), or *O*-benzotriazol-1-yl-*N,N,N',N'*-tetra-methyluroniumtetrafluoroborate (TBTU) with DIEPA in yields ranging 50 and 60%. For example, conversion with HATU gave **18** as a 2:1 mixture of diastereomers easily separated by chromatography on silica gel (Scheme 4.10) [9a].

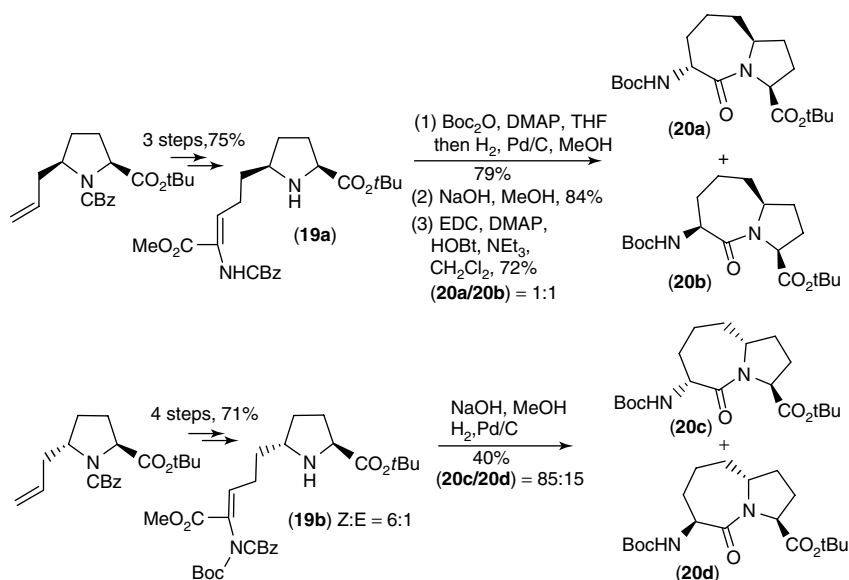
Moreover, this convenient method allowed an access to the two ring-fusion isomers with good yields.

Another application has been reported for the synthesis of *Stemona* alkaloids [9b].

The synthesis of “*trans*”- or “*cis*”-7,5-fused lactams **20a–d** was also efficiently achieved starting from the “*trans*”- or “*cis*”-5-allylproline derivatives **19a** or **19b**, respectively. The crucial final ring closure was performed using, for **19a**, a EDC/HOBt-promoted lactam formation and for **19b** a thermal basic lactam ring formation leading, in each case, to a mixture of the two possible epimers which were then easily separated by flash chromatography (Scheme 4.11) [9c].

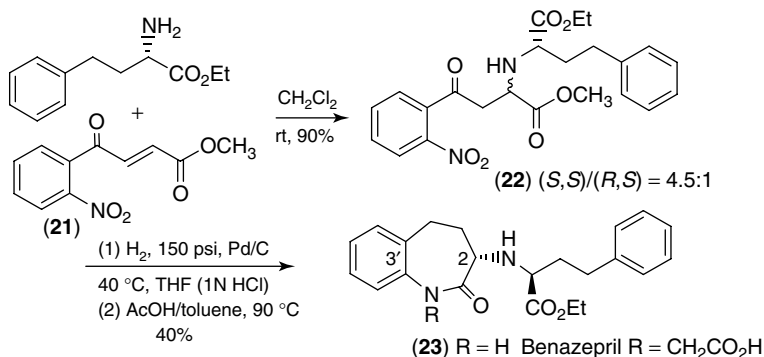


**Scheme 4.10** Synthesis of (7R)- or (7S)-pyrroloazepinone amino acid.



**Scheme 4.11** “Cis”- or “trans”- allyl-prolines as precursor of 5,7-fused lactams.

During the diastereoselective formal synthesis of benazepril·HCl [10], an antihypertensive drug, Yang *et al.* used an *in situ* intramolecular cyclization of an amino group with an ester function to create the bicyclic 6,7-fused skeleton. The precursor **22** was obtained by an asymmetric aza-Michael addition reaction of the L-homophenylalanine ethyl ester with the nitro compound **21** as a diastereoisomeric mixture. The diastereoselectivity of the 1,4-addition reaction depended upon the solvent, the temperature and the stoichiometry. Compound **22** was then reduced by a catalyzed Pd/C hydrogenation to its amino derivative which, under acidic treatment in toluene, led to the attempted (2*S*, 3'*S*)-caprolactam **23** easily transformed to benazepril (Scheme 4.12).



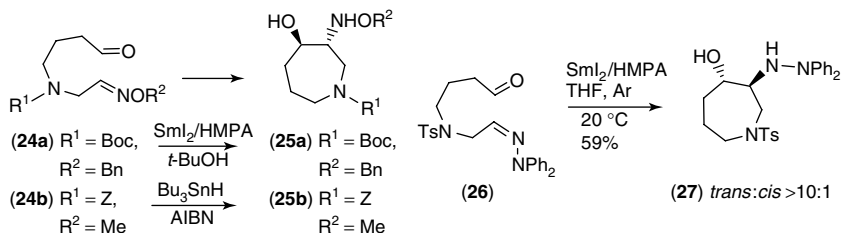
**Scheme 4.12** Diastereoselective formal synthesis of benazepril.

#### 4.1.2.2 Radical Cyclization

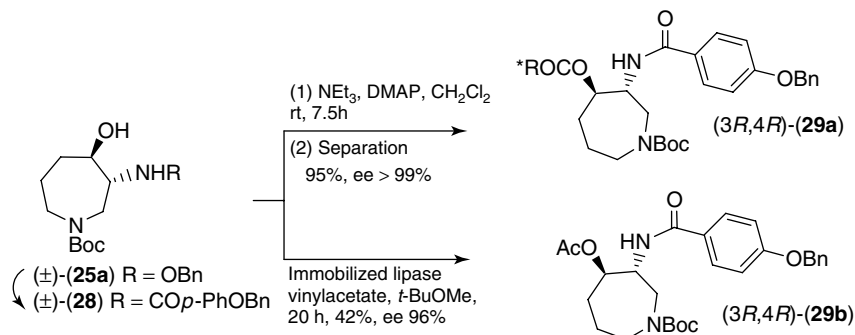
Numerous reports illustrated the construction of five- and six-membered heterocyclic rings by radical cyclization processes [11]. By contrast, less favorable cyclization to seven-membered ring has been less studied.

During their work devoted toward the total synthesis of (–)-balanol, Naito *et al.* [12a] described the radical cyclization of aldehyde **24a** with  $\text{SmI}_2$  in the presence of Hexamethylphosphoric triamide (HMPA) leading preferentially to the *trans* seven-membered ring **25a** in 46% yield (Scheme 4.13). Selectivity has been explained by chelation between the  $\text{Sm(III)(HMPA)}_n$  cation to the carbonyl and the oxime ether moieties. By the same way, Skrydstrup *et al.* [12b] synthesized the hexahydro-azepine **27** with high *trans* selectivity (10:1) by a  $\text{Sm(II)}$ iodide/HMPA induced pinacol-type cyclization of the corresponding acyclic hydrazone precursor **26**. Upon treatment with tributyltin hydride and 2,2'-azobis(2-methylpropionitrile) (AIBN), oxime ether **24b** underwent stannyl radical addition–cyclization with high selectivity to the major *trans*-hexahydro-azepine fragment **25b** in an *exo-trig* reaction pathway (Scheme 4.13) [12c].

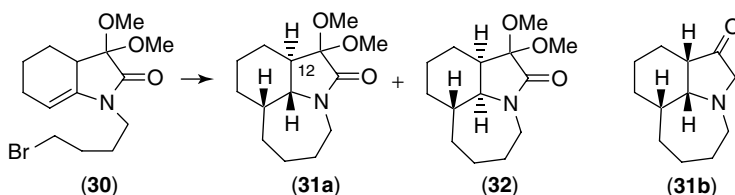
Finally, the enantiomerically pure hexahydro-azepine framework (3*R*, 4*R*)-**29a,b**, precursors of (–)-balanol, was obtained (i) after chemical optical resolution of the diastereomeric esters of the racemic alcohols **28** derived from **25** or (ii) by enzymatic optical resolution of **28** using the immobilized lipase *Pseudomonas* sp. (Scheme 4.14) [13].



**Scheme 4.13** Use of radical cyclization processes to azepine fragment of (–)-balanol.



**Scheme 4.14** Chemical or enzymatic optical resolution of ester ( $\pm$ )-28.

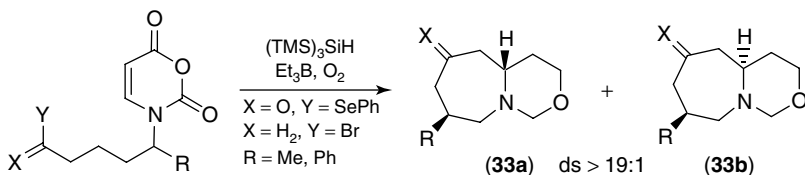


**Scheme 4.15** Radical cyclization to azepino-indoline of *Stemona* alkaloids.

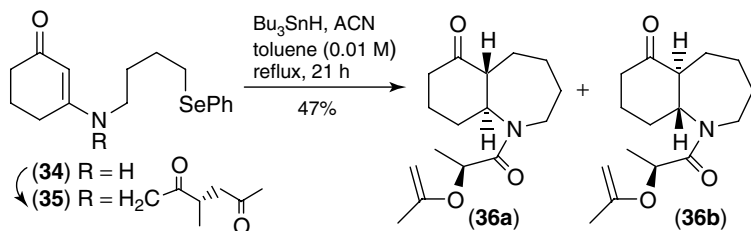
The azepino-indoline skeletons of the *Stemona* alkaloids have been efficiently prepared by radical cyclization [14] of hydroindolone **30** (Scheme 4.15). Thus, azepinoindolines **31a** and **32** were obtained in a 5:1 ratio and 85% overall yield using  $\text{Ph}_3\text{SnH/AIBN}$  in refluxing benzene under slow addition. The major formation of **31** arose from a 7-*endo-trig* radical cyclization process. Reduction of the lactam moiety followed by C-12 equilibration in acidic medium, permitted an access to **31b** owning another ring-fusion type of the *Stemona* compounds.

In 2000, Evans *et al.* [15] related the first examples of the intramolecular addition of acyl and alkyl radicals to oxauracil for the diastereoselective construction of *trans*-disubstituted-6,7-azabicycles **33** (Scheme 4.16).

Octahydrocyclopenta[*b*]azepines were obtained with excellent stereoselectivity by a 7-*endo* cyclization of various chiral vinylogous amides as reported by Cordes and Franke [16] in 2004. By this way, **34** was N-acylated with (*S*)-(-)-2-acetoxypriopionyl chloride to give chiral enaminone **35** in 82% yield. Treatment of **35** with  $\text{Bu}_3\text{SnH}$  in the presence of the radical initiator 1,1'-azo-bis(cyclohexanecarbonitrile) (ACN)



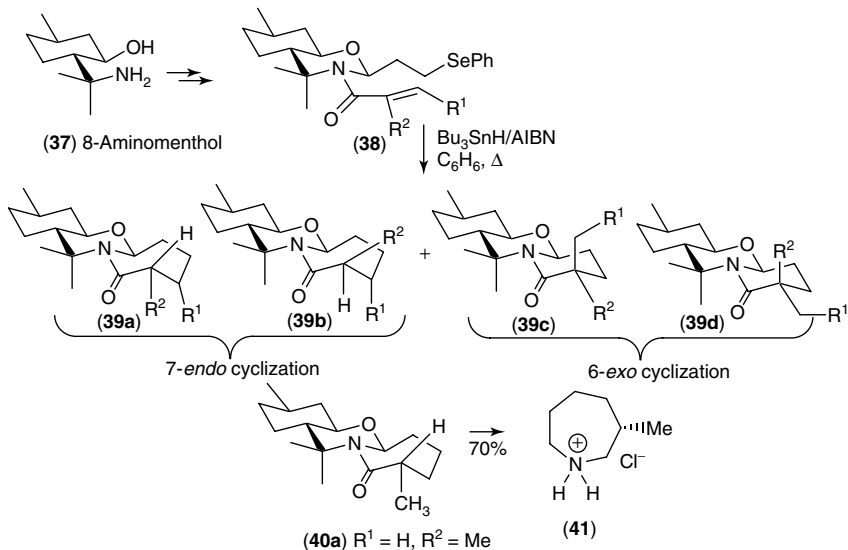
**Scheme 4.16** *trans*-Disubstituted 6,7-azabicycles.



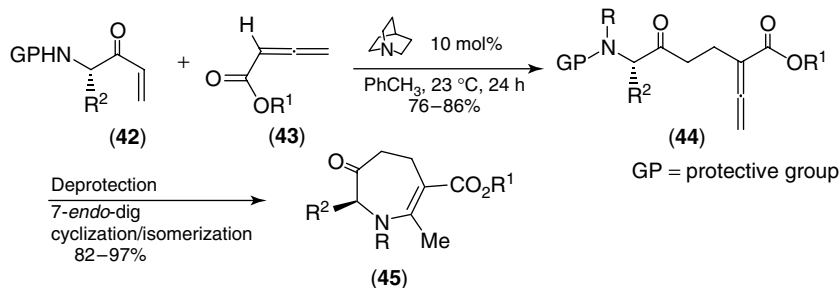
**Scheme 4.17** Diastereoselective synthesis of octahydrocyclopenta[*b*]azepines.

afforded the enantiopure azabicycles **36a,b** via a 7-*endo* ring closure in 47% yield (2:1 *ratio*). Changing the chiral appendage on the nitrogen atom of **35** (use of (1*S*)-(–)-camphanic chloride) permitted the formation of a single *trans*-fused octahydrocyclopenta[*b*]azepine in 44% yield with the relative stereochemistry of **36a** (Scheme 4.17).

An original and efficient approach to chiral 1,3-perhydrobenzoxazines **39** precursors of 3-substituted hexahydroazepines has been described. Thus, compounds **38**, generated in two steps from **37**, were engaged in an intramolecular radical addition promoted by Bu<sub>3</sub>SnH affording a nearly quantitative mixture of 7-*endo* **39a,b** and 6-*exo* **39c,d** cyclized compounds in a *ratio* depending upon the substituents at the  $\alpha$ -position of the double bond (Scheme 4.18). When R<sup>2</sup> = Me and R<sup>1</sup> = H, the cyclization step delivered a mixture of three products **40a–c** in favor of the 7-*endo* cyclization (75, 12, and 13% yields, respectively). The major one **40a** was further transformed into the enantiopure chlorhydrate (*S*)-3-methylperhydroazepine **41** in 70% yield [17].



**Scheme 4.18** Asymmetric approach to 3-substituted perhydroazepines.



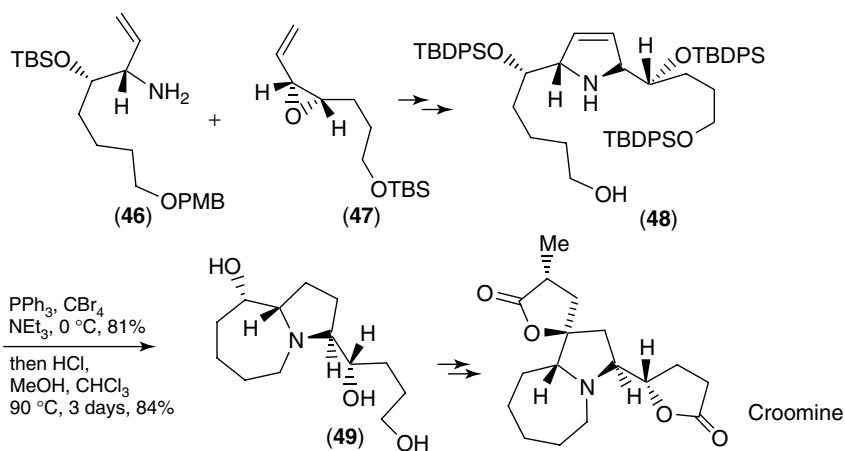
**Scheme 4.19** Azepine from 7-endo-dig cyclization of allenolate esters.

Vinyl ketones **42** derived from N-protected amino acids were coupled to allenolate esters **43** to furnish **44** which, after amine deprotection followed by 7-endo-dig addition of nitrogen to the electron-deficient sp-carbon of the allene and isomerization, afforded the azepines **45** in excellent yields (Scheme 4.19) [18].

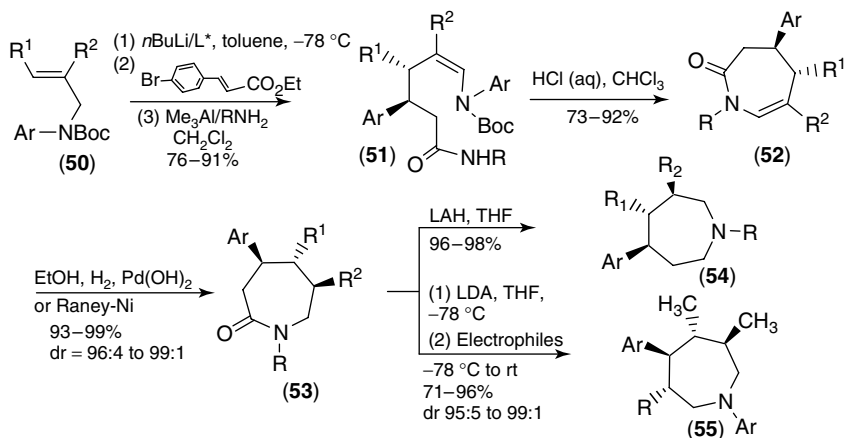
#### 4.1.2.3 Intramolecular Cyclization

Pyne *et al.* [19] developed a convergent preparation of the tricyclic B,C,D-ring core structure of croomine, a natural product possessing a pyrrolo[1,2-*a*]azepine skeleton. The key precursor **48** was prepared by a tandem chiral vinyl epoxide aminolysis/ring-closing metathesis (RCM) sequence starting from amine **46** and epoxide **47** and was then engaged in an intramolecular  $S_N2$  process to generate the 1H-pyrrolo[1,2-*a*]azepine **49** in a good yield of 68 % (Scheme 4.20).

Beak and Lee [20] reported an efficient asymmetric synthesis of 3,4,5- and 3,4,5,6-substituted hexahydroazepines **54** and **55** starting from enantio-enriched ene-carbamates **51** themselves obtained *via* a (–)-sparteine-mediated asymmetric lithiation of allyl amines **50** (Scheme 4.21).



**Scheme 4.20** Diastereoselective access to 1H-pyrrolo[1,2-*a*]azepine framework.



**Scheme 4.21** Asymmetric synthesis of 4,5,6- and 3,4,5,6-substituted azepanes.

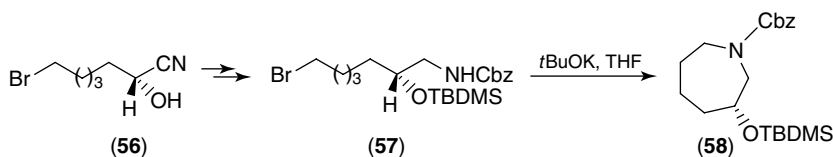
Acid hydrolysis of enamide **51** to aldehyde and subsequent cyclization led to the expected seven-membered ring system **52**. Hydrogenation of **52** afforded **53** possessing a *trans* stereochemistry at the C-6 position.

Reduction of lactam with  $\text{LiAlH}_4$  gave efficiently trisubstituted compounds **54**, whereas substitution at the C-3 position of **53** (for example,  $\text{R}^1 = \text{R}^2 = \text{CH}_3$ ,  $\text{R} = \text{Ar}$ ) by selected electrophiles provided tetrasubstituted azepanes **55** in good yields and high diastereoselectivity ( $\text{dr} > 95:5$ ) (Scheme 4.21).

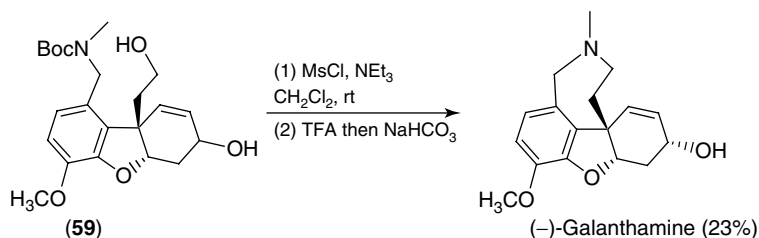
Optically active  $\omega$ -bromocyanohydrin **56** easily synthesized through an enantioselective (*R*)-oxynitrilase-catalyzed reaction from its corresponding  $\omega$ -bromoaldehyde was used as starting material to prepare azepan-3-ol **58** in a high enantiomeric excess. The crucial ring closure took place quantitatively using *t*BuOK on the (*R*)-protected bromoamino alcohol **57** with ee of 91% (Scheme 4.22) [21a].

Similar annelation process has been applied to the synthesis of the azepine core of (–)-galanthamine *via* the mesylate derivative of **59** but in modest yield (Scheme 4.23) [21b].

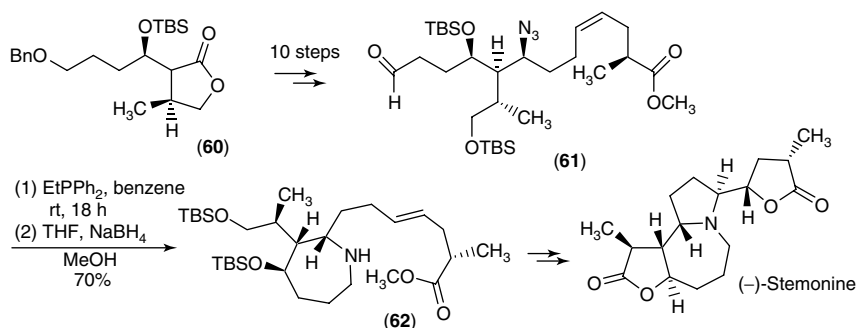
Williams *et al.* [22] reported in 2003 an enantioselective synthesis of (–)-stemone in which, the aza-seven-membered ring is formed by a Staudinger-aza-Wittig cascade reaction of an aldehyde-azide **61** followed by  $\text{NaBH}_4$  reduction. The chiral azide precursor **61** was itself easily prepared from the optically pure butyrolactone **60** through classical transformations.



**Scheme 4.22** Enantioselective synthesis of 3-hydroxyazepanes.



**Scheme 4.23** Synthesis of (-)-galanthamine.



**Scheme 4.24** Staudinger-aza-Wittig formation of the azepine ring.

Finally, iodine-induced cyclization of **62** led in a single step to the pyrrolidino-butyrolactone framework with good stereoselectivity which was then further transformed efficiently to the tricyclic fused (-)-stemonine (Scheme 4.24).

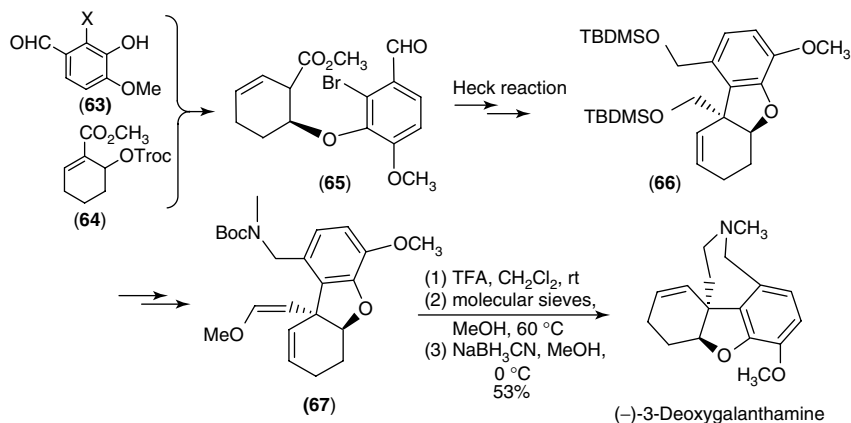
Reductive aminocyclization has been successfully adapted to the elaboration of seven-membered azacycles and we depict below some examples.

Palladium-catalyzed asymmetric allylic alkylation of halophenol **63** and  $\alpha$ ,  $\beta$ -unsaturated ester **64** led to intermediate **65** which was further transformed using a Heck cyclization process to the tricyclic compound **66**. Standard transformations afforded then compound **67** which underwent after Boc deprotection a final reductive intramolecular amination reaction to give (-)-3-deoxygalanthamine [23] in a good yield (Scheme 4.25).

Tri- and tetrahydroxyazepanes which were known as potent glycosidase inhibitors, were obtained in good yields from D-(-)-quinic acid. Oxidative cleavage of alcohols **68** or **69** afforded the corresponding dialdehydes which underwent a subsequent reductive aminocyclization using  $\text{BnNH}_2$  and  $\text{NaBH}(\text{OAc})_3$ . Hydrogenation gave azepanes **70** and **71**, which were in fact prepared in 10 steps with 17–34% yields from D-(-)-quinic acid (Scheme 4.26) [24].

Chiral nitrogen-containing seven-membered rings have been also efficiently prepared using 7-*endo* cyclization of olefins on *N*-acyliminium [25]. Thus, enamide **72** was obtained in three steps in a 1:1 ratio of two isomers from *N*-protected L-phenylalanine used as a chiral template. After separation by preparative high performance liquid chromatography (HPLC), isomer **72a** ( $\text{R}^1 = \text{CO}_2\text{Me}$ ,  $\text{R}^2 = \text{H}$ ) was efficiently cyclized by acidic treatment to the optically active azepine





**Scheme 4.25** Azepine ring from reductive intramolecular amination.

derivative **73** possessing the 5-7-6 tricyclic system of cephalotaxine alkaloid. The stereoselectivity of the reaction was excellent and was due to the equatorial conformation adopted by the phthalimide moiety in the acyliminium intermediate structure (Scheme 4.27) [26].

An asymmetric construction of the same 5-7-6 tricyclic core was reported through a Pictet–Spengler reaction [27]. Thus, conversion of the amido-alcohol **74** easily obtained from (*S*)-malic acid, to the lactams **75a,b** was realized in 70% yield with a good regioselectivity using triflic acid *via* an acyliminium cyclization process (Scheme 4.28).

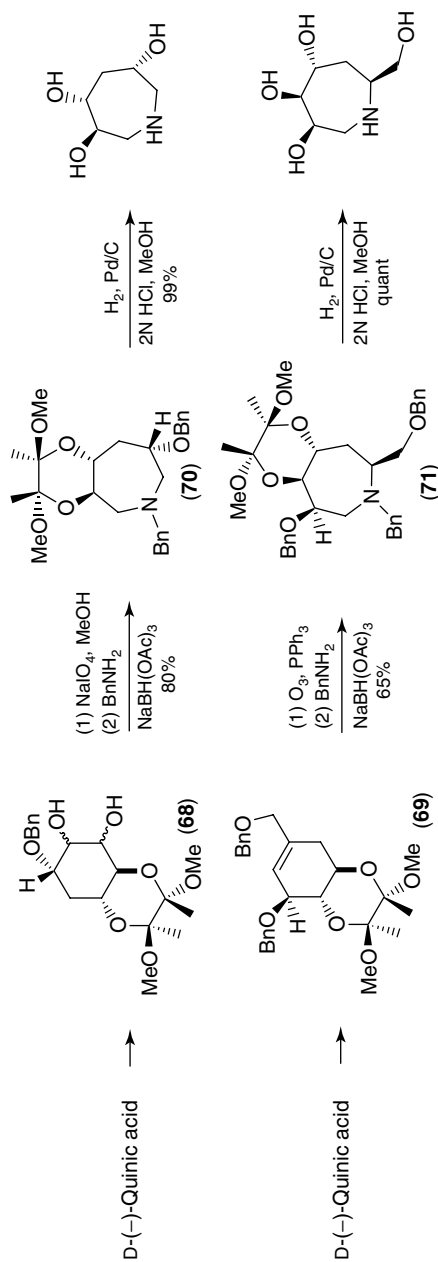
The Pictet–Spengler reaction was also efficiently applied by Chida *et al.* [28] to the stereoselective synthesis of (+)-galanthamine starting from D-glucose which allowed the formation of the optically pure cyclohexene ring of the amide precursor **76**. Upon treatment with *para*-formaldehyde in the presence of trifluoroacetic acid (TFA), **76** generated the known seven-membered tetracyclic derivative **77**, precursor of the alkaloid in 67% yield (Scheme 4.29).

Using the same methodology, the azepine ring of (–)-lycoramine was elaborated by Malachowski *et al.* [29] in 2007 in the first enantioselective synthesis of this alkaloid.

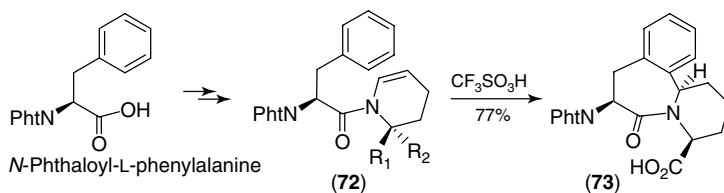
Even if the Pummerer-cyclization applied to seven-membered ring systems is less efficient than for the six-membered analogs, benzazepine derivatives that are difficult to obtain by others methods have been synthesized using this reaction and a review discussed their preparation [30].

Others cyclization processes have been adapted to the edification of azepane framework.

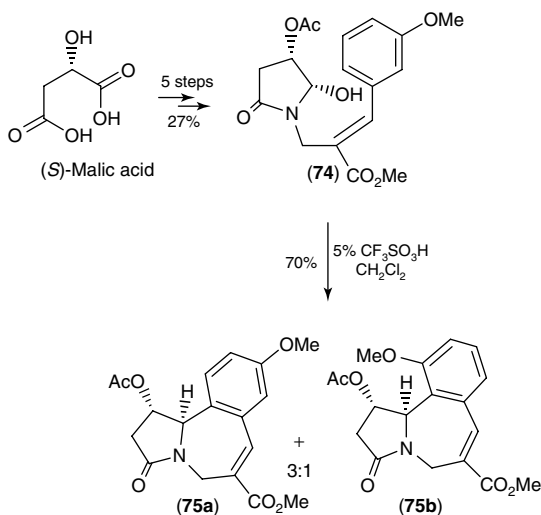
For example, Hayes *et al.* [31a] created the azepine ring of the tetracyclic core of (–)-cephalotaxine [31b], using an intramolecular Heck cyclization. Thus, cyclization of **78**, prepared from *N*-Boc-L-proline ester in seven steps and 7% overall yield, mediated by Pd catalyst afforded the sole formation of the endocyclic olefin **79** in 62% yield (Scheme 4.30).



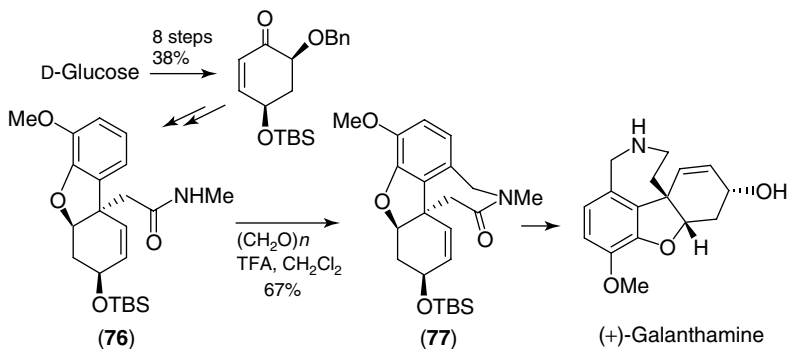
**Scheme 4.26** Asymmetric synthesis of trihydroxy- and tetrahydroxyazepanes.



**Scheme 4.27** Cyclization of olefins on *N*-acyliminium.

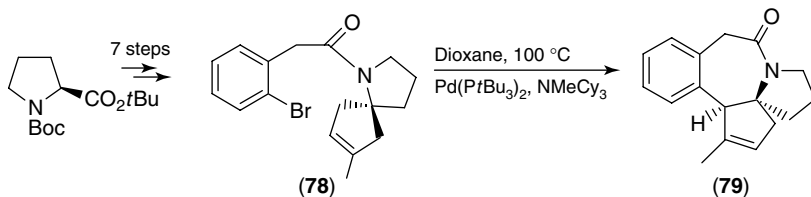


**Scheme 4.28** Pictet–Spengler approach to the azepane ring.

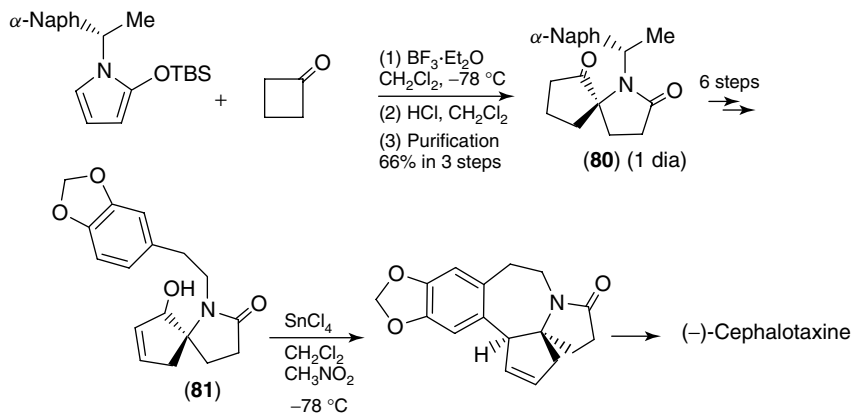


**Scheme 4.29** Asymmetric synthesis of (+)-galanthamine *via* a Pictet–Spengler cyclization.

Azaspiro[4.4]nonane framework which constitutes the C/D ring moiety of cephalotaxine has received particular interest. Thus, compound **80**, prepared in an enantiomerically pure form using an original semipinacolic rearrangement of an  $\alpha$ -hydroxyiminium ion by Royer *et al.* [32], was chosen as a pivotal compound in



**Scheme 4.30** Heck cyclization to seven-membered lactam.



**Scheme 4.31** Lewis acid cyclization to seven-membered azepane.

the preparation of (–)-cephalotaxine and analogs; the final azepine ring closure of **81** precursor was then performed using Lewis acid (Scheme 4.31).

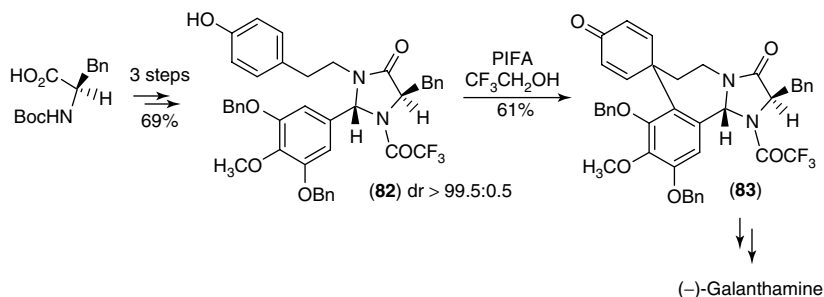
#### 4.1.2.4 Oxidative Phenol Coupling Reaction

Optically active (–)-galanthamine has been efficiently prepared from 1-tyrosine methyl ester and 3,5-dibenzyloxy-4-methoxybenzaldehyde using as key step a phenolic oxidative coupling to create the seven-membered ring [33a].

An improved synthesis of the same alkaloid has been also depicted [33b,c] starting from the protected substrate **82**, issued from (*R*)-*N*-Boc-D-phenylalanine, and using, in this case, phenyliodine(III)*bis*-(trifluoroacetate) as the oxidant instead of Mn(acac)<sub>3</sub> for the oxidative coupling. In this case, the spirodienone **83** was obtained in 61% yield and was then further transformed into (–)-galanthamine. Formation of the last stereocenters of the final tetracycle is controlled by the chirality of the (*R*)-*N*-Boc-D-phenylalanine which, in fact, promotes a total asymmetric induction (Scheme 4.32).

#### 4.1.2.5 The Ring Closure Metathesis

Because of increasing strain in the transition state and entropic influences, medium-sized rings, for example, 8–10 membered rings are the most difficult to prepare. Among all the cyclization reactions developed to obtain these



**Scheme 4.32** Phenolic oxidative coupling to aza-seven-membered nucleus.

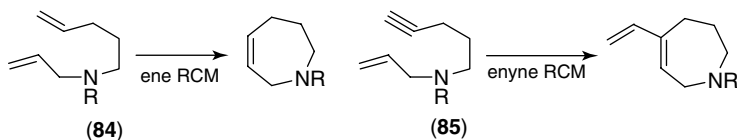
structures, the RCM provided an alternative efficient pathway to form heterocyclic systems, in particular nitrogen-containing compounds and even to prepare fused-nitrogen subunits present in the natural product area. Therefore, this method has been extensively developed these last years. In fact, numerous syntheses of the seven-membered ring of azepine-compounds using RCM [34] have also been investigated, all the approaches varying only on the strategy developed to prepare the diene and the enyne precursors **84** and **85** and on the type of catalysts used (Scheme 4.33). To facilitate the cyclization, several features were installed in the substrates **84** or **85** providing conformational constraint. These steric hindrances were generally obtained by using preexisting rings (like oxazolidine ring) or acyclic conformational constraints.

We introduce here, different routes developed for the RCM cyclization leading to the azepine precursors **84** and **85**.

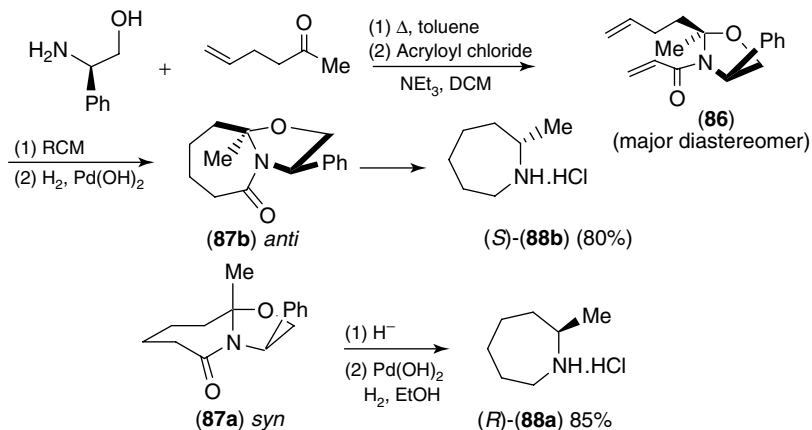
Chiral 2-substituted azepines **88** were prepared from *bis*-olefinated oxazolidines **86** *via* the [5,3,0]-bicyclic lactam scaffold **87** [35]. These chiral templates were obtained by azeotropic condensation of 5-hexene-2-one with (*R*)-phenylglycinol followed by treatment with acryloyl chloride. An RCM ring closure of the major 2-(*R*)-*N*-acryloyl oxazolidine **86** using 5 mol% of Grubbs ruthenium catalyst followed by reduction of the resulting double bond afforded the 5,7-bicyclic lactam **87b** in 98% yield as a single product (61% from (*R*)-phenylglycinol).

Stereoselective reduction followed by hydrogenolytic cleavage of the *N*-benzyl moiety gave finally the perhydroazepine (*S*)-**88b** in 80% yield. The same procedure applied to the *syn* epimer gave the (*R*)-**88a** in 85% yield (Scheme 4.34).

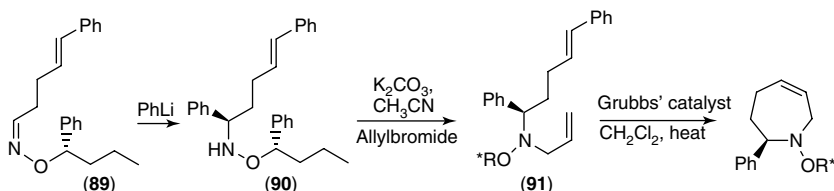
Chiral aldoxime ether (*S*)-**89** acted as chiral precursor of allylamine **91** in the RCM approach of 2-substituted tetrahydroazepines. Conversion of **89** to the hydroxylamine **90** followed by *N*-allylation using allylbromide in the presence of  $K_2CO_3$  led to **91** which underwent an RCM reaction by heating in the presence of



**Scheme 4.33** RCM applied to azepine derivatives.



**Scheme 4.34** Asymmetric synthesis of perhydroazepine starting from chiral oxazolidines.



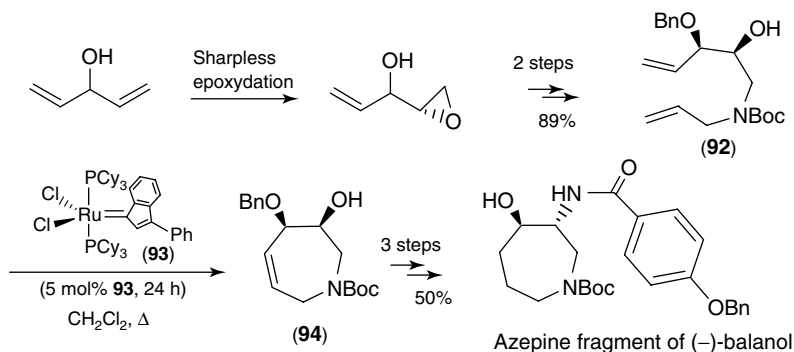
**Scheme 4.35** Azepines from chiral aldoxime ether.

Grubbs catalyst giving the expected seven-membered heterocycle but in only 9% yield (Scheme 4.35) [36].

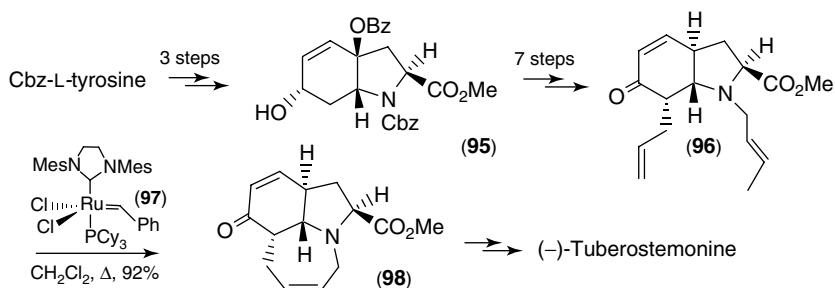
Fürstner and Thiel reported in 2000 [37] a short (eight steps) enantioselective route for the hexahydro-azepine moiety of (–)-balanol with an excellent overall yield. The approach needed the preparation of the diene **92** which was obtained through a four-step sequence starting with a Sharpless epoxidation of divinylcarbinol. RCM reaction of **92** was then conducted in the presence of the ruthenium indenylidene complex **93** giving the tetrahydroazepine **94** in 87% yield (Scheme 4.36).

The first total synthesis of the complex polycyclic *Stemona* alkaloid (–)-tuberostemonine, known for its properties against pulmonary tuberculosis and bronchitis, was reported by Wipf *et al.* [38] The synthesis of its [1,2-*a*]azepine core was on the basis of an RCM reaction of **96** to form the azepane skeleton. Pivotal intermediate **96** was formed by selective transformations of the building block **95**, while the latter was prepared from Cbz-*L*-tyrosine which served as a scaffold for the installation of nine of the 10 stereogenic carbons of tuberostemonine. Heating a solution of **96** in the presence of the ruthenium catalyst **97** led to the tricyclic precursor **98** of the alkaloid in 92% yield (Scheme 4.37).

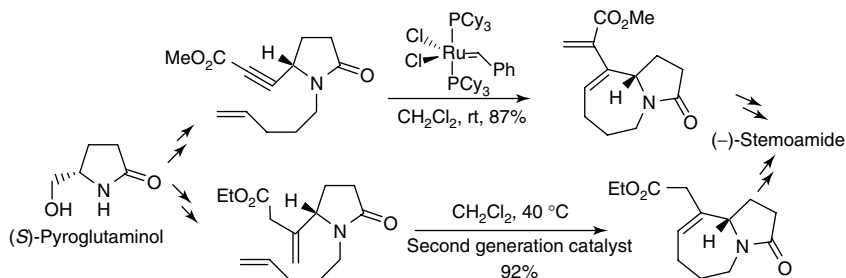
Intramolecular Grubbs' olefin metathesis has also been used to obtain chiral fused 7-5- or 5-7-bicyclicolactams in good yields [39a]. For example, the pyrrolo[1,2-*a*]azepine core of (–)-stemoamide was prepared either by an ene [39b]



**Scheme 4.36** Access to azepine fragment of (-)-balanol using chiral divinylcarbinol and RCM.



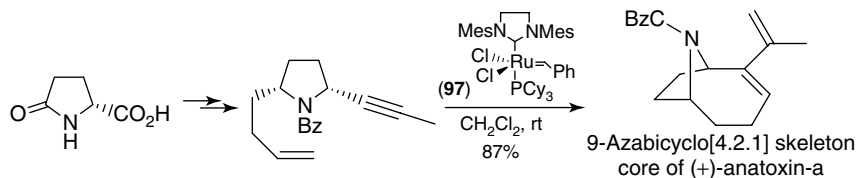
**Scheme 4.37** Synthesis of [1,2-*a*]azepine core of (-)-tuberostemonine by RCM.



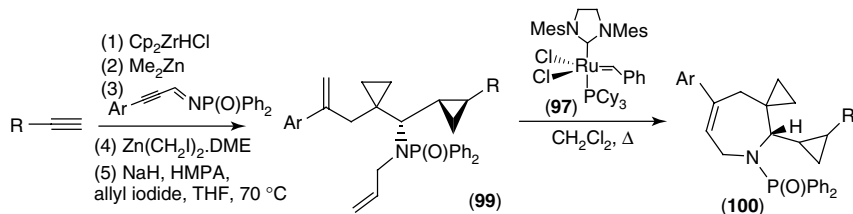
**Scheme 4.38** Pyrrolo[1,2-*a*]azepine core of (-)-stemoamide.

or an enyne RCM [40a] reaction starting from protected (*S*)-pyroglutaminol, which introduced the chirality (Scheme 4.38).

Others successful applications of intramolecular enyne metathesis have been reported. Among them, we can mention the enantiospecific access to the 9-azabicyclo [4.2.1] skeleton core of (+)-anatoxin-a [40b] starting from *D*-methyl pyroglutamate and using, in this case, as the key enyne a *cis*-2,5-disubstituted pyrrolidine (Scheme 4.39).



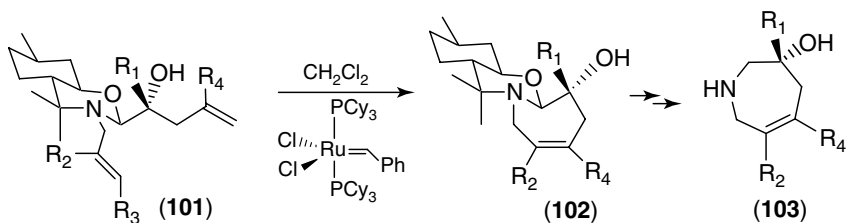
**Scheme 4.39** Enantiospecific synthesis of (+)-anatoxine-a.



**Scheme 4.40** Diastereoselective approach toward spiroazepines.

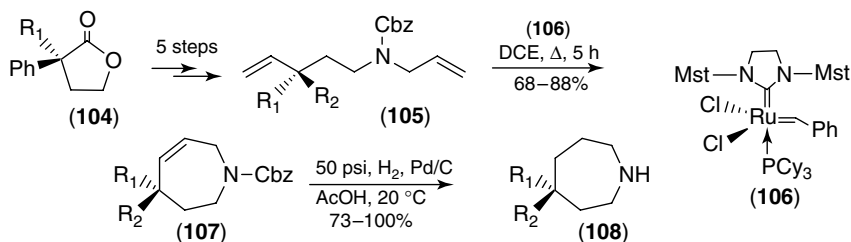
$\omega$ -Unsaturated dicyclopropylmethylamines obtained by multicomponent condensation of *N*-diphenylphosphinoylimines, alkynes, zirconocene hydrochloride, and diiodomethane constitutes interesting building block in the synthesis of spiro-azaheterocycles [41]. Thus, the *N*-alkylated C,C-dicyclopropylmethylamines **99** underwent a ring-closing reaction using second-generation Grubbs catalyst (10 mol%) leading to 1*H*-azepines **100** in 63–84% yield (Scheme 4.40).

Chiral alcohols **101** prepared in good diastereoselectivity (*de* > 90) from (–)-8-aminomenthol underwent RCM reaction with Grubbs' catalyst to afford 2-benzoylperhydro-1,3-benzoxazines **102**. The mol% of the catalyst used (4–15 mol%) together with the temperature of the reaction (20 °C to reflux) and its duration (20–240 h) depended of the nature of the substituent of the double bond [42]. The final transformation of **102** into the enantiopure 2,3,4,7-tetrahydro-1*H*-azepin-3-ols **103** was performed in three steps and 44–56% yield by (i) reductive ring opening of the N,O-acetal moiety with aluminum hydride, (ii) oxidation with pyridinium chloro-chromate (PCC) of the menthol, and (iii) basic cleavage (KOH, tetrahydrofuran (THF)/methanol) (Scheme 4.41).



**Scheme 4.41** Asymmetric synthesis of 2-benzoylperhydro-1,3-benzoxazines.





**Scheme 4.42** Chiral 4-mono and 4,4'-disubstituted tetrahydroazepines.

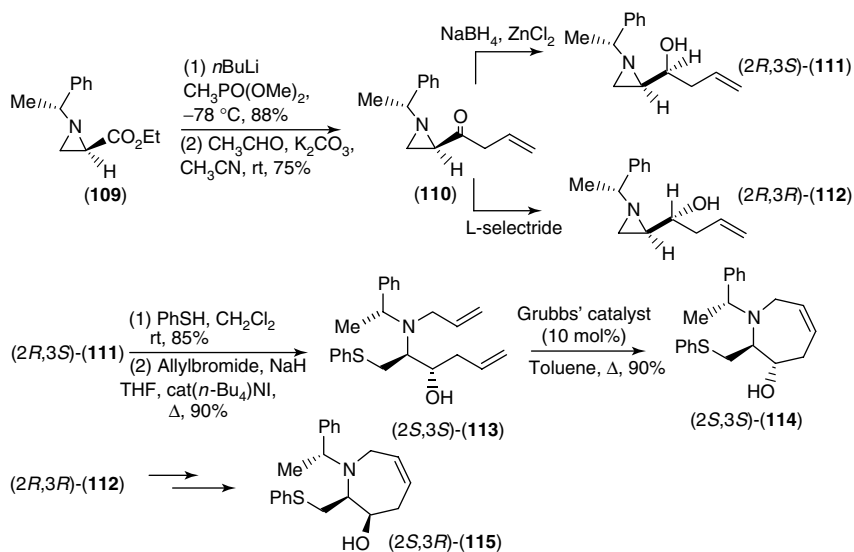
A general strategy for the preparation of 4-mono and 4,4'-disubstituted tetrahydroazepines **108** was developed by Merschaert *et al.* [43] starting with chiral, commercially available or easy to prepare lactones **104**. The key aza derivatives **105** issued from **104** underwent then an RCM reaction using Grubbs' catalyst **106**, leading to the unstable seven-membered heterocycles **107** (68–88%) (Scheme 4.42).

Hydrogenolysis and concomitant reduction of the double bond furnished the tetrahydroazepines **108** in nearly quantitative yields (Scheme 4.42).

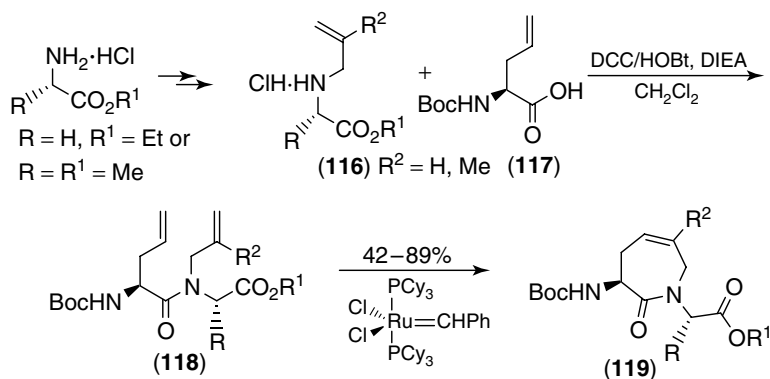
1,2,3,6-Tetrahydro-1*H*-azepin-3-ols are intermediates in the asymmetric synthesis of azasugars. A method for their stereoselective preparation was reported by Lee *et al.* [44a] starting from optically pure aziridine **109** and using, as the final ring closure pathway, an RCM reaction. Thus, the (2*R*)-aziridine **109**, generated by reaction between (*R*)-(+)- $\alpha$ -methylbenzylamine and ethyl 2,3-dibromopropionate, was transformed in 73% yield to the allyl ketone **110** using an Horner–Wadsworth–Emmons olefination. A stereoselective reduction of the ketone function led to the *erythro* alcohol (2*R*, 3*S*)-**111** in 96% yield using  $\text{NaBH}_4/\text{ZnCl}_2$  in MeOH and to the *threo* (2*R*, 3*R*)-**112** exclusively by treatment with *L*-Selectride. The *N*-allylamine **113** was then obtained after regioselective ring opening of the chiral aziridine with a thiolate anion at the less sterically hindered C-1 position followed by alkylation with allylbromide. Subsequent RCM reaction of the resulting *bis*-olefin with second-generation Grubbs catalyst afforded enantiomerically pure (2*S*, 3*S*)- and (2*S*, 3*R*)-azepinols **114** and **115** from (2*R*, 3*S*)- and (2*R*, 3*R*)-alcohols **111** and **112**, respectively (Scheme 4.43).

Another tetrahydro-(1-*H*)-azepine-3-ol of similar structure has been also described using a similar methodology, the unique difference being in the synthesis of the chiral precursor which was here obtained through an Evans aldol reaction [44b].

Gmeiner *et al.* [45] developed a useful synthesis of (2*S*)-7-membered cyclic dipeptides mimics **119** using an RCM cyclization promoted by ruthenium catalyst of precursors **118**. The metathesis precursor **118** was readily available through a *N,N'*-dicyclohexylcarbodiimide (DCC)/HOBT-promoted peptide coupling of glycine derivative **116** with the secondary amine **117**, which was in turn prepared from glycine or alanine esters (Scheme 4.44).



**Scheme 4.43** Chiral azepines from ring opening of aziridines followed by RCM reaction.



**Scheme 4.44** Chiral 2-amino seven-membered lactams from amino acids.

#### 4.1.3

##### Cycloaddition Methods

Just a few cycloaddition methods were depicted to generate aza-seven-membered ring. The most commonly developed was the [4 + 3] cycloadditions which took place with moderate to high yields with complete regio and diastereoselectivity. Others attractive approaches exploited either 1,3-dipolar cycloaddition of nitrone or intramolecular Diels–Alder reactions (IMDA).

## 4.1.3.1 [5 + 2] Cycloaddition

A concise approach to the C-D-E part **121** of HHT, was reported in 2001 by Booker-Milburn *et al.* [46a] Intramolecular [5 + 2] photocycloaddition of substituted maleimide **120** led, after reopening of the four-membered ring, to azepine framework which was obtained as a mixture of two diastereoisomers (yield 75%, de 3.5:1) (Scheme 4.45).

The same cyclization process was applied also with success to the synthesis of the tetracyclic core of neotuberostemonine [46b] and of oxetanol-fused azepines [46c].

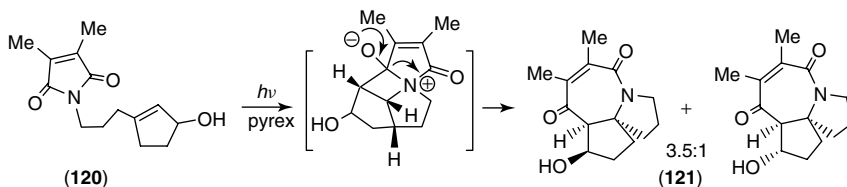
## 4.1.3.2 [4 + 3] Cycloaddition

Thermal cycloaddition reaction of alkenyl Fischer chiral carbene **122** derived from (–)-menthol with oxime **123** resulted in the formation of diastereomers **124** and **125** in 87% yield and a 7:3 ratio. Changing for (+)-menthol afforded the same diastereomers in 80% yield and a reverse 3:7 ratio. Crystallization of the major one followed by acid hydrolysis allowed the isolation of enantiomerically pure azepinones (Scheme 4.46) [47].

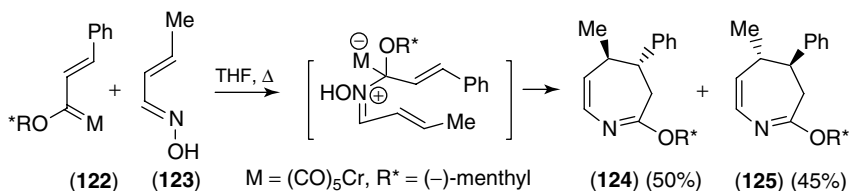
## 4.1.3.3 Nitron Cycloaddition

Formation of azepane skeleton has been also envisaged through intramolecular 1,3-dipolar cycloaddition of nitron to olefine, followed by N–O reductive cleavage processes.

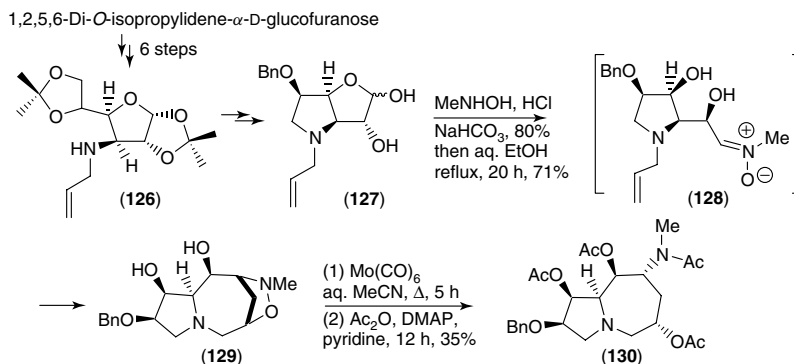
An example of this method [48a] consists in the preparation of the pyrrolo[1,2-*a*]azepine framework **130** by *N*-allylcarbohydrate nitron cycloaddition. The precursor **126** was classically obtained in six steps from the 1,2,5,6-di-*O*-isopropylidene- $\alpha$ -D-glucofurannose and was then transformed to the furanoside-fused pyrrolidine **127** as a 2:1 anomeric mixture in 73% yield using standard reactions. On treatment with *N*-methylhydroxylamine hydrochloride/ $K_2CO_3$



**Scheme 4.45** Diastereoselective access to azepines derivatives by [5 + 2] photocycloaddition.



**Scheme 4.46** Enantiomerically pure azepinone using [4 + 3] cycloaddition process.



**Scheme 4.47** Nitron cycladdition to azepine ring.

**127** gave *exclusively* the bridged isoxazolidine **129** *via* the nitron **128** in a 71% yield. Cleavage of this isoxazolidine ring was realized using  $\text{Mo(CO)}_6$  in aqueous acetonitrile and led to the azabicyclic ring in 35% yield (Scheme 4.47).

Intramolecular nitron cycladdition allowed also an access to aminohydroxazepines starting from amino acids as chiral pool [48b].

#### 4.1.3.4 Intramolecular Diels–Alder Reactions (IMDA) – [4 + 2] Cycloaddition

The intramolecular version of the Diels–Alder reaction [49] has been applied with success to the elaboration of the seven-membered ring of the *Stemona* alkaloids.

Thus, Jacobi and Lee [50a] described an original concise synthesis of (–)-stemoamide using an IMDA-*retro*-Diels–Alder (DA) reaction of the propyne derivative **132** obtained in three steps from (*S*)-oxazole lactam **131** easily prepared on multigram scales with no racemization from (*S*)-L-pyroglutamic acid. Thermolysis of (*S*)-**132** in diethylbenzene at reflux gave the tricyclic azepine compound **134** owing the natural configurations and issued from rearrangement of tetracyclic derivative **133**. Subsequent selective reduction with  $\text{NaBH}_4/\text{NiCl}_2$  afforded finally (–)-stemoamide (Scheme 4.48).

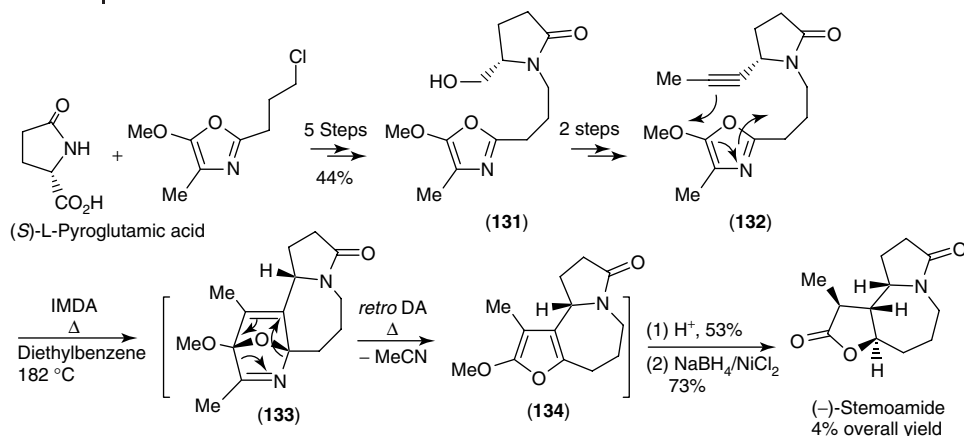
This cyclization mode has been applied with success to the synthesis of (–)-stenine, another member of the *Stemona* alkaloids [50b].

#### 4.1.4

##### Ring Transformation Methods

Much attention has been focused upon the preparation of seven-membered rings incorporating one nitrogen atom using (i) rearrangement of cyclohexanones (Beckmann, Schmidt reactions or its intramolecular version, the Boyer reaction) or (ii) expansion of preexisting smaller rings. Sometimes, thermal and photochemical rearrangements are also combined with retro-aldol reaction.

We report in this section the asymmetric syntheses of azepines framework on the basis of all these methods [51], and, for better understanding, we present here



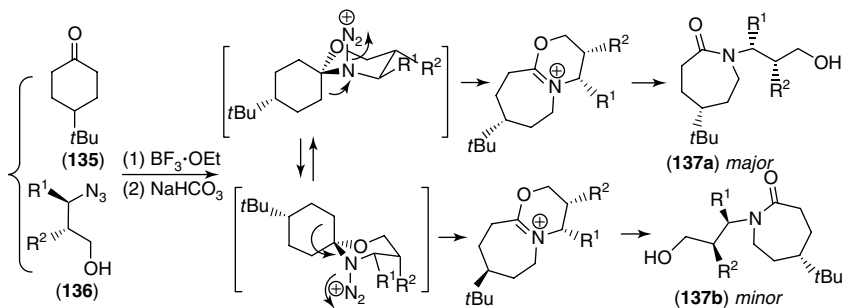
**Scheme 4.48** Azepine ring from an IMDA reaction.

the literature results in two parts; the first one describing “classical reactions” of rearrangement and the second part introducing an access to seven-membered aza nucleus by enlargement of nitrogenous cycle of variable size.

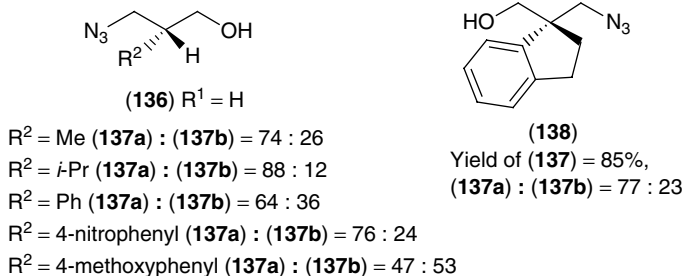
#### 4.1.4.1 Classical Methods

Aubé *et al.* [52a,b] converted ketone **135** to lactams **137a,b** in good yield and stereoselectivity (for example, when  $R^1 = \text{Ph}$  and  $R^2 = \text{H}$ , **137a/137b** = 7.2:1) via an “*in situ*-tethering” strategy using hydroxyalkyl azides **136** and a Lewis acid. The stereoselectivity may be explained by the equatorial attack of azide on the oxonium ion followed by migration of the *pseudo*-axial bond antiperiplanar to the leaving  $\text{N}_2$  substituent (Scheme 4.49).

In a further study, the authors [52c] showed that the stereoselectivity of the reaction could be modulated by electronic and conformational effects. The *ratio* of isomers **137a,b** depended upon the nature (alkyl or aryl) of the  $R^2$ -substituents of the hydroxyl-azide **136** and even upon the electronic nature of the  $R^2$ -aryl group. Effective enhancement of selectivity was also detected using a linker containing a quaternary carbon like **138** (Scheme 4.50).



**Scheme 4.49** Chiral caprolactam by asymmetric nitrogen insertion process.



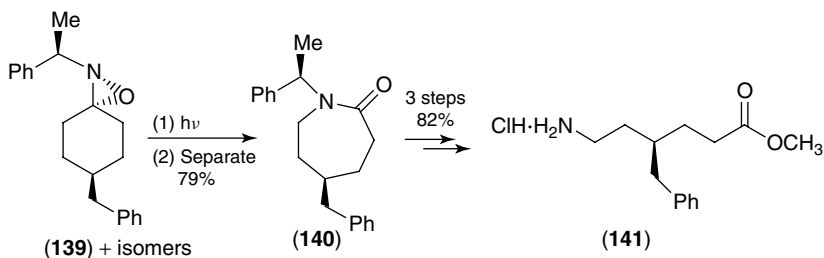
**Scheme 4.50** Influence of the azide in the formation of the caprolactams.

This method allowed the stereoselective synthesis of substituted caprolactams by ring expansion of chiral ketones in a one-pot procedure with only one work-up providing diastereomers which were easy to separate. Moreover, the removal of the chiral group on the nitrogen could be accomplished efficiently and depended only upon the structure. A systematic study of this asymmetric Schmidt reaction has been published in 2003 by Aubé *et al.* [52d]

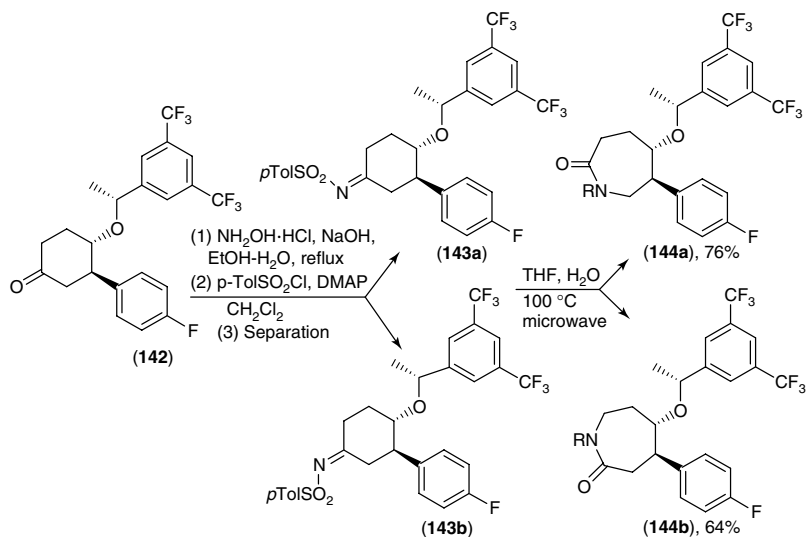
During their work devoted to the synthesis of a series of Gly–Gly-derived macrocycles containing a *cis*-aminocaproic acid (Aca) tether, Aubé *et al.* [52e] needed to prepare several linkers **141** which could be easily obtained by acid hydrolysis followed by esterification of chiral caprolactams. An example is depicted below: the caprolactam **140** resulted in excellent yield from light induced ring opening (photo-Beckmann rearrangement) of the chiral oxaziridines mixture **139**. The mixture of lactams thus obtained could be easily separated and the major one, **140**, afforded linker **141** with an excellent enantiomeric excess of 98% (Scheme 4.51).

Thermal regioselective Beckmann rearrangement (microwave 100 °C) [53a] of separated *p*-toluenesulfonyloximes **143** obtained from ketone **142** led to isomeric lactams **144** (Scheme 4.52).

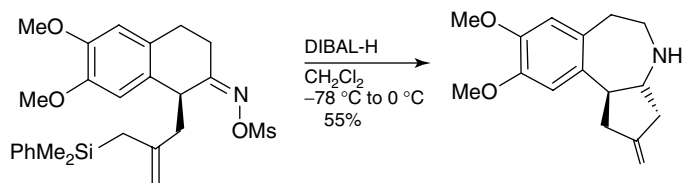
An asymmetric Beckmann rearrangement/allylsilane-terminated cation cyclization cascade was used to elaborate the seven-membered ring of cephalotaxine framework (Scheme 4.53) [53b].



**Scheme 4.51** Photolysis of oxazolidines to chiral caprolactams.



**Scheme 4.52** Modified Schmidt rearrangement to caprolactams.



**Scheme 4.53** Asymmetric Beckmann rearrangement.

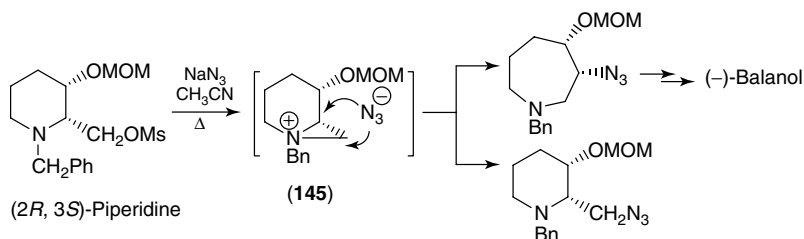
#### 4.1.4.2 Ring Expansion

The synthesis of azepines derivatives has been efficiently envisaged by ring expansion of preexisting smaller rings in particular piperidine, pyrrolidine, azetidinium salts, and pyranoside.

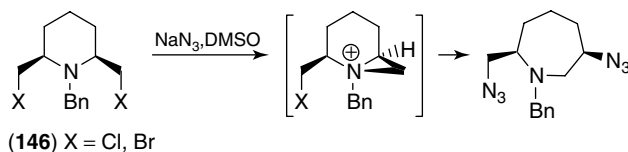
During their study toward the synthesis of balanol, Kato and Morie [54] developed the ring expansion of a *cis*-aziridinium cation **145** to form, together with the normal displacement piperidine derivative, the aza-seven-membered ring *via* an S<sub>N</sub>2-type attack of the azide anion at the methyne carbon (Scheme 4.54).

Using the same approach starting from the symmetrical piperidine **146**, Brechbiel *et al.* [55] synthesized diastereomerically azepanes in about 90% yield by ring expansion using  $\text{NaN}_3$  in Dimethyl-sulfoxide (DMSO) with good stereoselectivity; only the *cis* isomer was obtained *via* a backside attack at the methine carbon (Scheme 4.55).

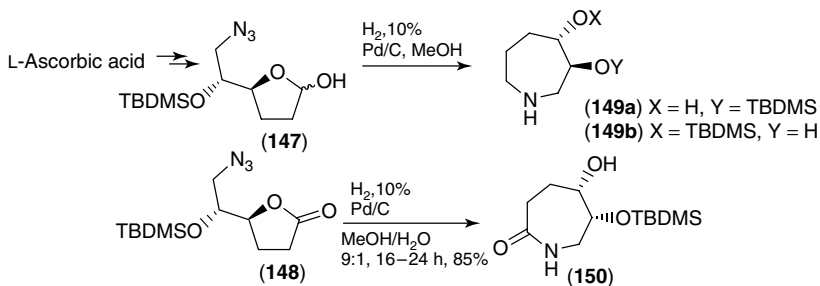
It is well known that azidolactols underwent reductive ring enlargement in the presence of hydrogen to yield azepanes [56]. Applied to chiral lactol **147** and lactone **148**, obtained from the transformation of L-ascorbic acid, this reaction allowed the preparation of 3,4-disubstituted azepanes **149** and (5*S*, 6*S*)-caprolactam **150**, precursors of (+)- and (–)-balanol in excellent yields (Scheme 4.56) [57].



**Scheme 4.54** Chiral azepine fragment of balanol *via* piperidine ring expansion.



**Scheme 4.55** Piperidine ring expansion to azepanes.



**Scheme 4.56** Chiral lactones to substituted caprolactam.

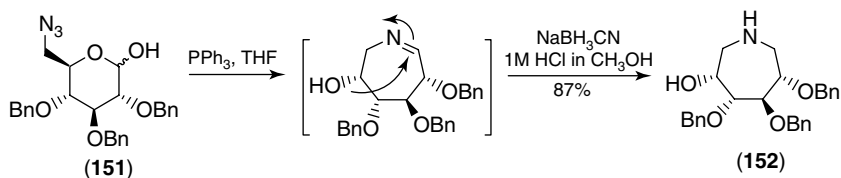
Polyhydroxyazepanes (seven-membered iminocyclitols) [58], have been synthesized using an analogous method. For example, iminocyclitol **152** could be obtained starting from chiral azidolactol **151** derived from  $\alpha$ -D-glucopyranoside, by a tandem Staudinger intramolecular aza-Wittig ring expansion with triphenyl phosphine in 87% yield (Scheme 4.57) [58c].

Chemo-enzymatic synthesis starting from benzylpyranoside produced polyhydroxyazepane **153** in only two steps using aqueous media and proceeding on a gram scale (Scheme 4.58) [58d].

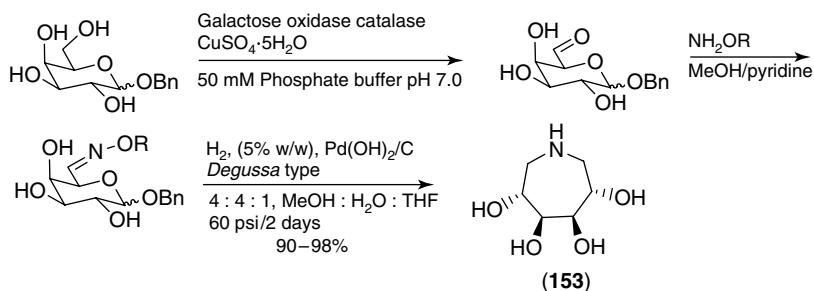
In 2003 [59a], a simple and versatile method for the enantio- and diastereoselective synthesis of 2-substituted- and 2,7-disubstituted-3-aminoazepanes **156** and **157** was reported using a tandem ring enlargement/alkylation or reduction process starting from 2-cyano 6-oxazolopiperidine **154** (Scheme 4.59). Bicyclic aминаl **155**, derived from **154** by standard reactions, could be then transformed into the *trans*-azepane **156** in yields between 80% and 96%.

This method permitted the stereoselective preparation of the indolyldiamine **156** ( $R^1 = N$ -methyl indole), carba-analog precursor of the tetracyclic azepane eudistomine, an antiviral and antitumoral compound (Scheme 4.58) [59b].

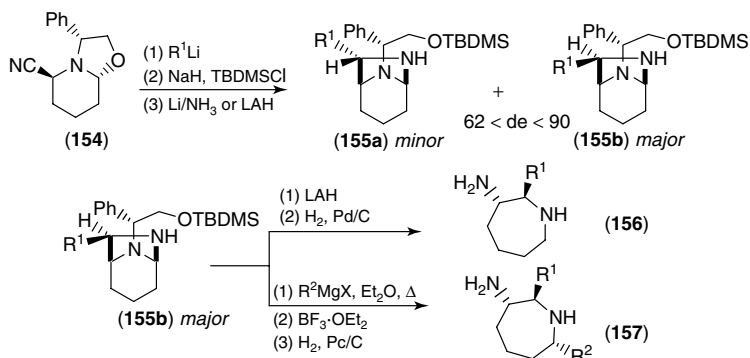




Scheme 4.57 Seven-membered iminosugar.



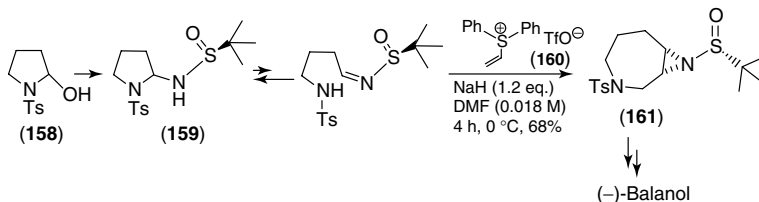
Scheme 4.58 Chemo-enzymatic synthesis of seven-membered iminocyclitol.



Scheme 4.59 Enantioselective synthesis of 2-substituted- or 2,7-disubstituted-3-aminoazepanes.

On the other hand, treatment of **154** with iso-butyl or benzyl Grignards, which act as nucleophilic reagents, led to 2,7-disubstituted-3-aminoazepanes **157** in good yields and excellent diastereoselectivity ( $\text{de} > 95\%$ ) (Scheme 4.59).

The chiral hexahydro-azepine **161** constitutes an interesting potential azepine derivative for the synthesis of more functionalized compounds. It could be rapidly prepared by ring opening of  $\gamma$ -aminoaldehyde **158** with (*R*)-*tert*-butylsulfonamide followed by reaction with diphenyl vinyl sulfonium **160**. Derivative **161** existed as a 3:1 mixture of diastereomers easily separated by flash chromatography (Scheme 4.60). Further deprotection of the major aziridine has permitted, for example, the synthesis of the known precursor of (–)-balanol [60].



**Scheme 4.60** Vinyl sulfonium salt in asymmetric synthesis of aziridine fused azepine.

The two-carbon ring expansion of heterocyclic compounds is an original method to elaborate azepine derivatives, which has been successfully used in the preparation of 3-oxo-pyrrolidine and azetidine substrates (*vide infra*).

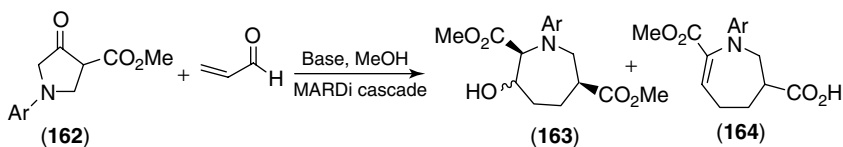
Thus, a Michael Aldol Retro-Dieckmann (MARDi) sequence was used in converting 3-oxo-pyrrolidine **162** and acrolein in the presence of MeOH into a mixture of hydroxyazepane **163** (dr = 1.6:1) and tetrahydro-azepine **164** in 36% overall yield (Scheme 4.61) [61].

Ring expansion of enantiomerically pure 2-alkenylazetidinium trifluoromethanesulfonate salts **165** under basic condition permitted a clean access to enantiomerically pure substituted azepanes **166a** and **166b** with variable diastereoselectivity at the C-2 position through a [2,3] sigmatropic shift (Stevens rearrangement) of the ylide generated after selective deprotonation  $\alpha$  to the ester group (Scheme 4.62) [62].

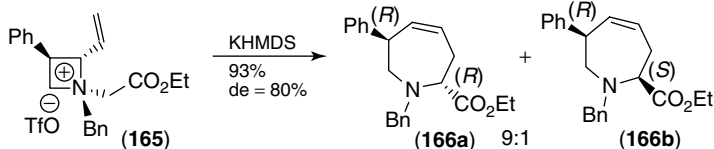
#### 4.1.4.3 Substitution of Already Formed Heterocycles

Most of the syntheses of complex azepines derivatives associated with pharmaceutically important activities depicted in the literature have, as a corner stone, an already formed aza-seven-membered ring which has been formed from caprolactam derivatives [51b].

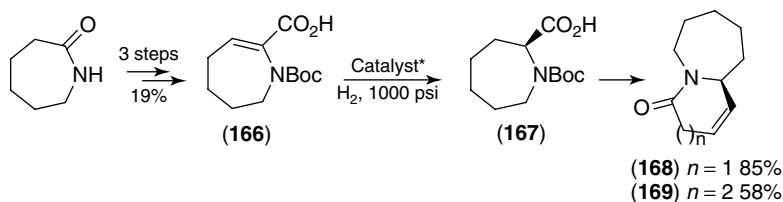
For example, asymmetric synthesis of fused seven-membered lactams **168** was reported employing an asymmetric hydrogenation of the caprolactam derivative **167** with  $[\text{Rh}(\text{COD})\text{-(+)-(2S, 5S)-Et-DUPHOS}]\text{OTf}$ . This approach allowed



**Scheme 4.61** Diastereoselective MARDi cascade to azepine ring.



**Scheme 4.62** Ring expansion of chiral 2-alkenylazetidinium trifluoromethanesulfonate salts.



**Scheme 4.63** Fused chiral seven-membered lactams from caprolactam.

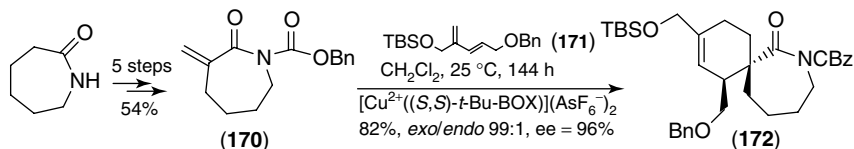
the preparation of the (*S*)-*N*-protected-homopipericolic acid **168** in 98% yield and 90% ee. Acid **168** is then further transformed into the azabicyclic compounds **169a,b** in a four-step sequence using as a key reaction an RCM ring formation (Scheme 4.63) [63].

Construction of the azaspiro[5.6]dodec-9-ene **172**, a part of pinnatoxin A, a marine toxin of shellfish and dinoflagellate, has been efficiently elaborated by an asymmetric Diels–Alder reaction of the  $\alpha$ -methylene caprolactam **170** with the diene **171** using chiral Lewis acid.

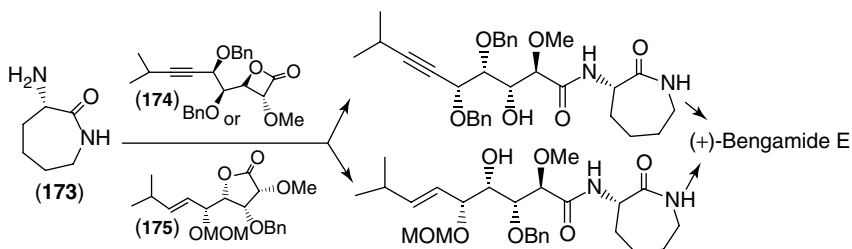
The precursor **170** was readily obtained in five steps and 54% overall yield from caprolactam itself (Scheme 4.64). The enantioselectivity observed in this synthesis arose from the chirality of the copper complex formed and the *exo* selectivity was due to the unfavorable steric interactions between the substituent in the diene and the chiral ligand of copper complex in the *endo*-transition state [64].

The ongoing interest in bengamides and analogs as clinical candidates for cancer chemotherapy has prompted the preparation of a lot of various original 2-*N*-substituted-aminocaprolactams by introducing the polyfunctional substituent either on the commercially available (2*S*)-aminocaprolactam, or, on the readily accessible chiral 4-hydroxy-2-aminocaprolactam [51b], [65a]. Thus, for example, synthesis of (+)-bengamide E relied on ring opening of substituted acetylenic  $\beta$ -lactone **174** by (*S*)-3-aminocaprolactam **173**. Subsequent stereoselective reduction of the acetylenic moiety led to (+)-bengamide E. A similar approach was also reported starting with  $\gamma$ -lactone **175** (Scheme 4.65) [65b,c,d,e].

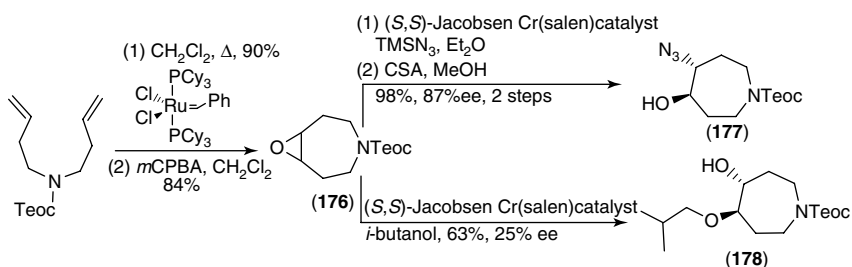
The *meso* epoxide azepine compound **176** prepared by an RCM reaction of *N*-Teoc-*N*, *N*-bishomoallylamine constitutes a versatile substrate for the synthesis of hexahydro-disubstituted azepines. When treated with trimethylsilyl azide in the presence of the Jacobsen Cr(salen) catalyst epoxide **176** furnished, after cleavage of the silyl ether, the hydroxyazide **177** in 98% yield and 87% ee in two steps. Epoxide opening of **176** with *i*-butanol under the same reaction conditions led to



**Scheme 4.64**  $\alpha$ -Methylene caprolactam, precursor of the azaspirocyclic part of pinnatoxin A.



**Scheme 4.65** Use of (*S*)-2-aminocaprolactam for the synthesis of azepine derivatives.



**Scheme 4.66** Epoxide ring opening to chiral 4-hydroxy azepines.

the alcohol **178** in 63% yield but in this case with a modest enantiomeric excess (25%) (Scheme 4.66) [66].

## 4.2 Substituted Azocines

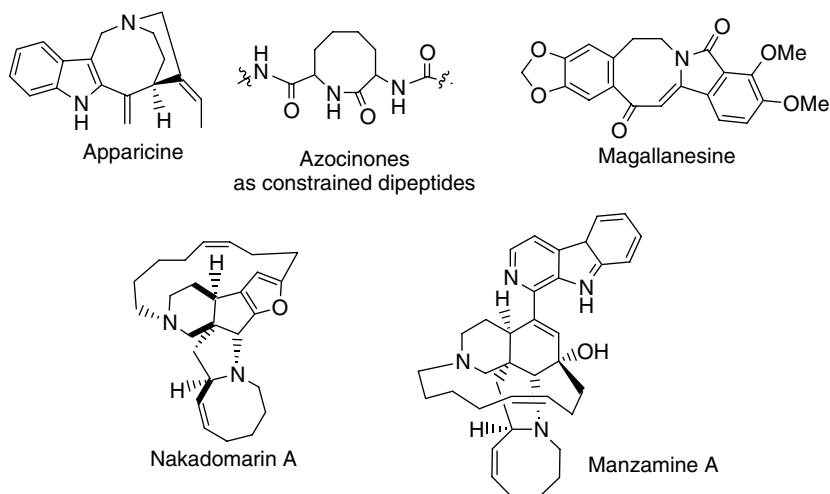
The commonly encountered azocines ( $\pi$ -equivalent heterocyclic analogues of cycloocta-tetraenes), fully or partly reduced, constitute a part of the skeleton of natural products with complex structures like apparicine, magallanesine, nakadomarin A and manzamine A, an indole alkaloid isolated from marine sponges with antitumor and antibiotic activities (Scheme 4.67) [67a].

Many of the synthetic azocine derivatives have found application as therapeutic agents because of their broad spectrum of properties [1d] together with the favorable flexibility of their ring which allow binding with species.

In particular azocin-2-ones have been used as sedatives, anticonvulsant, antihypertensive agents and the disubstituted ones find application as peptide analogues to mimic the type VI  $\beta$ -turn conformation of natural polypeptides [67b,c].

Fused-azocines like benzofuroazocines possess important activity in the central nervous system [67d] and the pyrrolidino- and piperidino-azocines could serve as intermediates in alkaloids synthesis [67e].

The preparation of this aza-eight-membered ring, especially in highly functionalized form, using classical cyclization from an alicyclic chain by intramolecular



**Scheme 4.67** Azocine compounds.

nucleophilic substitution remains very specific and is often slow and hampered by unfavorable enthalpies and entropies of the reaction [68].

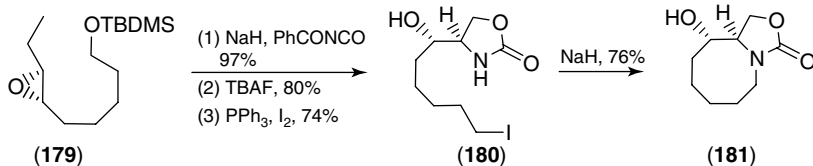
Diverse other synthetic methodologies have been developed on the basis of intramolecular substitution, ring contraction or enlargement such as fragmentation of fused 5/5-ring system, [2 + 2] photochemical, or thermal cycloaddition reactions, and most recently by powerful RCM reaction that sometimes requires high dilution conditions for successful conversion.

#### 4.2.1

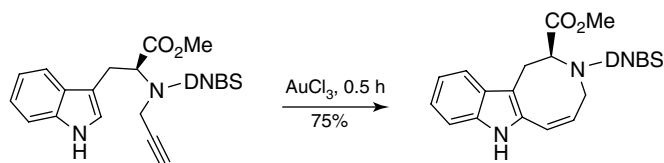
##### Azocines from Intramolecular Nucleophilic Substitution

For example, azocine **181** has been efficiently synthesized in 76% yield by intramolecular basic substitution of the oxazolidinone iodide **180** easily obtained by exposure of the Sharpless epoxide **179** to sodium hydride and benzoylisocyanate [69] (Scheme 4.68).

Recently, fused indolo-azocines have been prepared by an intramolecular cyclization of alkyne derivatives of tryptamine catalyzed by  $\text{AuCl}_3$  in an 8-*endo*-dig process (Scheme 4.69) [70].



**Scheme 4.68** Intramolecular cyclization to azocine.



DNBS = dinitrobenzenesulfonyl group

**Scheme 4.69** Cyclization to azocines catalyzed by gold.

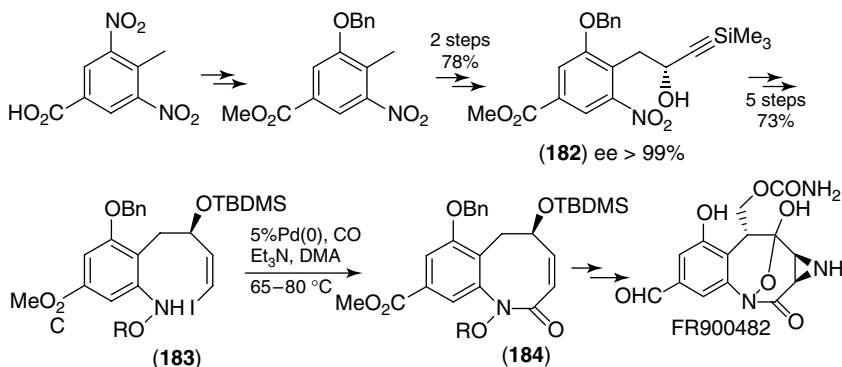
Asymmetric synthesis of benzazocine framework **184**, an advanced intermediate in the synthesis of FR900482, has been achieved by Pd-catalyzed carbonylation-insertion-cyclization of an arylhydroxylamine with a tethered vinyl iodide **183**. Compound **183** was easily prepared from commercially available 3,5-dinitro-*p*-toluic acid in seven steps and 57% yield *via* the enantiomerically pure secondary alcohol **182** (ee > 99%). The best parameters for this reaction were a temperature ranging 65–80 °C, *N,N*-dimethylacetamide as solvent and Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> as catalyst. By this way, eight-membered rings were obtained in 64–78% yield (Scheme 4.70) [71].

#### 4.2.2

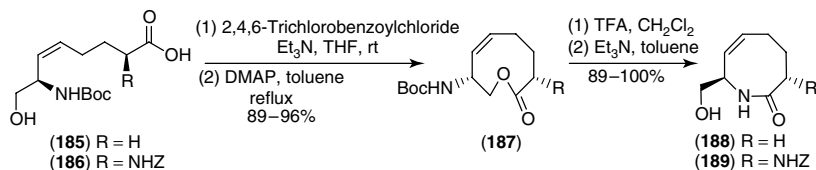
##### Ring Transformations Methods

Formation of substituted eight-membered lactams by intramolecular rearrangement of 5,6-dehydro-2-oxocanone **187** provided an access to either *trans*-3,8-disubstituted or 3-substituted eight-membered lactams **188** and **189**, from acids **185** or **186** in 89% and 85% yields, respectively (Scheme 4.71) [72].

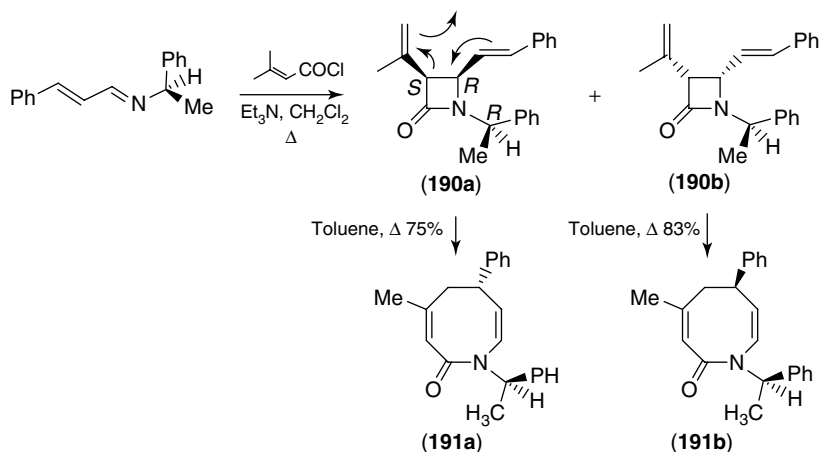
Cope rearrangement of enantiomerically pure 2-azetidinone-tethered dienes **190**, prepared as single *cis*-diastereomers from cinnamylideneimine derived from *R*-(+)- $\alpha$ -methylbenzylamine, allowed the preparation of optically pure eight-membered lactams **191** in good yields (Scheme 4.72) [73].



**Scheme 4.70** Asymmetric approach to FR900482 benzazocine.



**Scheme 4.71** 2-Azacanones by lactone-to-lactam ring contraction of 2-oxonanones.

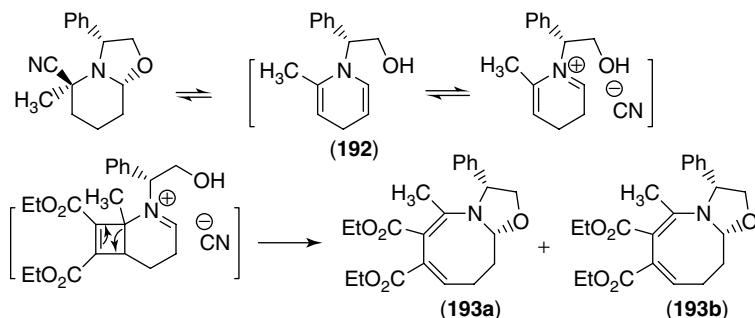


**Scheme 4.72** Eight-membered lactams via [3,3] sigmatropic rearrangement of azetidinones.

#### 4.2.3

##### Cycloaddition Approaches to Azocines

Thermal [2 + 2] cycloaddition reaction between 1,4-dihydropyridine **192** and diethylacetylenedicarboxylate in the presence of  $\text{Al}_2\text{O}_3$ , afforded a cyclobutene intermediate which underwent an electrocyclic ring opening resulting in the formation of the two diastereomers **193a** and **193b** in 30 and 44% yields, respectively (Scheme 4.73) [74].



**Scheme 4.73** Synthesis of tetrahydro-azocines by cycloaddition of latent 1,4-dihydropyridines.

Another cycloaddition process allowing the stereoselective synthesis of 3,7-disubstituted azocin-2-one has been developed by Shea *et al.* [75].

Thus bridged bicyclic oxazinolactam **195b** was obtained as a single diastereomer in 85% yield (100% ds) by a type 2 intramolecular *N*-acylnitroso Diels–Alder reaction of the hydroxamic acid **194** ( $R^2 = \text{H}$ ,  $R^1 = \text{Bn}$ ) in the presence of  $n\text{-Bu}_4\text{NIO}_4$ . For example, bicycle[5.3.1]oxazinolactam **195a** could be transformed to the *trans*-azocinone **196** by alkylation followed by cleavage of the N–O bond, whereas oxazinolactam **195b** was converted to the *cis*-compound **197**. In the case of (*R*)-C-4 substituted hydroxamic acid **194** ( $R^1 = \text{H}$ ,  $R^2 = \text{Bn}$ ), Diels–Alder oxidation with  $n\text{-Bu}_4\text{NIO}_4$  provided in 84% yield two diastereomers **195d** and **195e** in a 3.7:1 ratio in favor of the *syn* compound **195e** (Scheme 4.74).

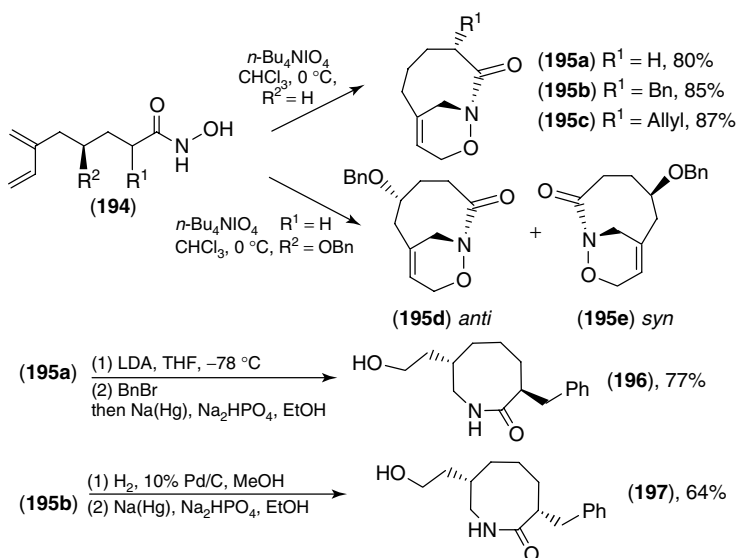
#### 4.2.4

##### Ring-Closing Metathesis

Synthesis of medium-ring cyclic amines has been reported by Schrock *et al.* [76a] using an asymmetric ring-closing metathesis (ARCM) reaction catalyzed by Mo catalysts in the absence of solvent. Thus, compound **198** in the presence of 5 mol% **199** delivered optically pure amine **200** (ee > 98%) in 93% yield (Scheme 4.75).

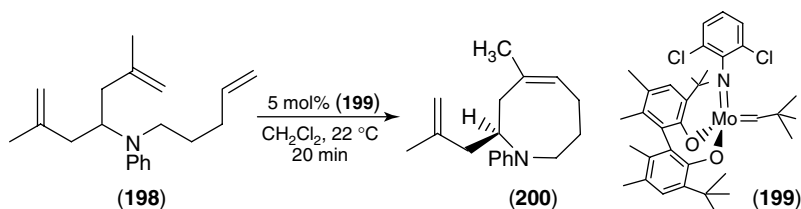
Enantioselective syntheses of benzaocine compounds (e.g. (+)-FR900482) have been completed with this method using Grubbs' catalyst [76b].

A library of constrained chiral eight-membered ring lactams has been prepared in high yields from two L-allylglycine residues **201** (Agy) employing an RCM reaction with first generation benzylidene ruthenium catalyst [77] (Scheme 4.76).

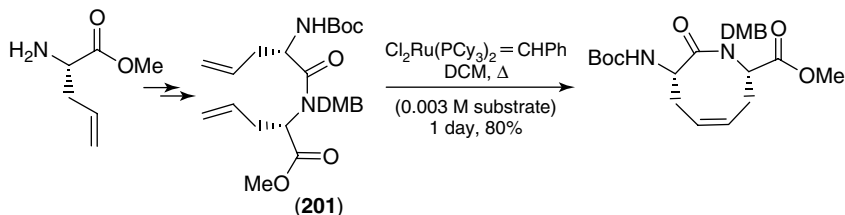


**Scheme 4.74** Medium-ring lactams by diastereoselective intramolecular *N*-acylnitroso Diels–Alder reaction.





**Scheme 4.75** Mo-Catalyzed asymmetric ring-closing metathesis to eight-membered amines.



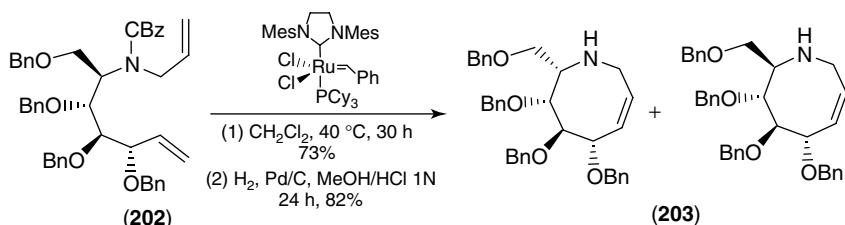
**Scheme 4.76** Synthesis of eight-membered ring lactam by RCM reaction.

In view of the high potential of iminosugars for drug discovery and considering the increase of conformational flexibility that the eight-membered ring has brought, a synthesis of iminoalditols **203** has been developed from aminoheptenitols **202** using an RCM reaction.

The chirality at C-3, C-4 and C-5 came from the commercially available starting material, 2,3,4,6-tetra-O-benzyl-D-glucopyranose precursor of **202**. The epimer mixture at C-2 was easily separated by ion-exchange chromatography (Scheme 4.77) [78].

Enantiopure 1,2,3,4,5,8-hexahydroazocin-3-ols have been prepared by distereoselective addition (de > 95) of Grignard reagents to chiral perhydrobenzoxazines followed by an RCM reaction of the 1,9-azadienes thus obtained [42].

Moreover, the RCM reaction was adapted successfully to the synthesis of the eight-membered rings of more complex compounds, namely the alkaloids Manzamine A, Ircinal and Nakadomarin A in moderate to good yields [79].



**Scheme 4.77** Synthesis of eight-membered iminoalditols.

## 4.3

## Substituted Large Nitrogen-Containing Rings

Among the large nitrogen-containing rings, the substituted nine-membered derivatives deserve particular attention. In fact, these nitrogen heterocycles, well known as azonine derivatives, are found as subunits in natural and pharmaceutically important molecules [1c,d], [51b] like rhazinilam, which interfere with tubulin polymerization, tuberostemonone, and cleavamine (Scheme 4.78).

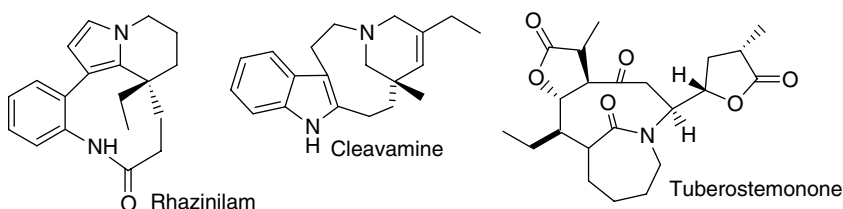
Moreover, these medium-sized constrained ring systems, in particular the azocinones, serve as key intermediates in the synthesis of bicyclic amino compounds like indolizidines or quinolizidines [80] by selective transannular ring contractions.

The easiest way to generate a nine-membered nitrogen ring, for example lactam azocinones, consists of an intramolecular reaction of  $\omega$ -amino esters. But, even using activating groups either at the carboxyl or amino functions the cyclization was often low yielding (Scheme 4.79) [81].

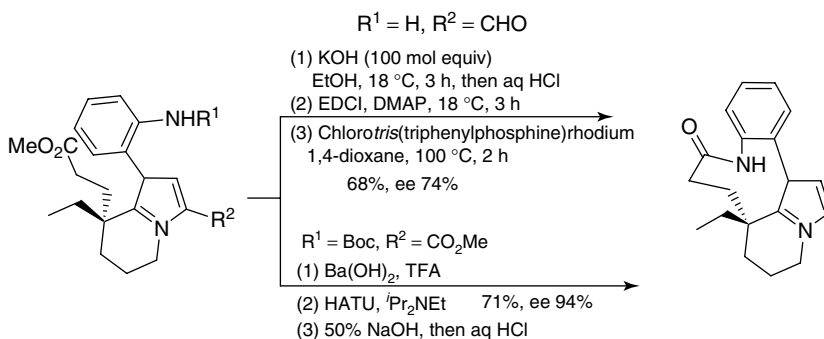
This process has been also used in indole series and allowed the synthesis of cleavamine [81c] and 5a-*homo*-vinblastine [81d].

Because of the interesting biological properties of rhazinilam, a lot of methods have been devoted to the synthesis of its skeleton.

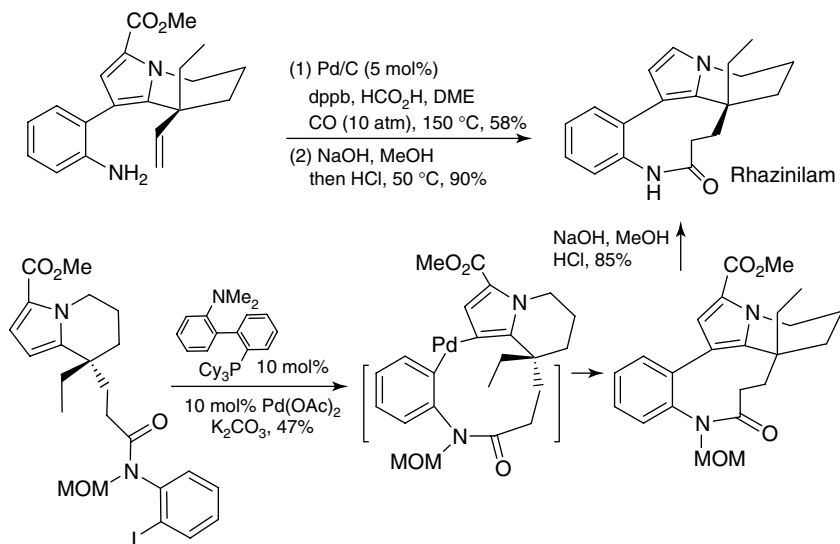
Among them, palladium-catalyzed intramolecular coupling [82a] and carbon homologation to macrolactam *via* palladium-catalyzed carbonylation [82b] were the more efficient and afforded the nine-membered aza ring in good yields (Scheme 4.80).



Scheme 4.78 Substituted Azonines.



Scheme 4.79 Enantioselective synthesis of (–)-rhazinilam.

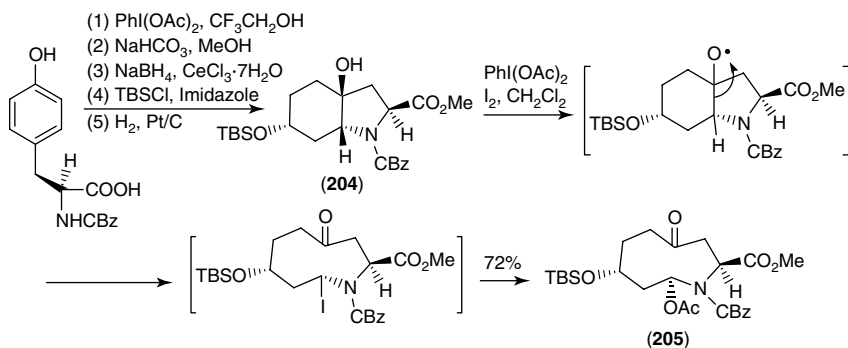


**Scheme 4.80** Palladium-catalyzed coupling to rhazinilam skeleton.

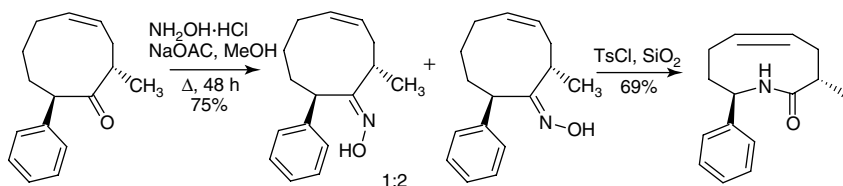
Others methodologies have been developed to elaborate azocine derivatives in particular the ring enlargement of a smaller ring by N or C atoms insertion using fragmentation or rearrangement reactions. For example, oxidative cyclization of Cbz-tyrosine permitted the preparation of the hydroindole **204**, which when exposed to a mixture of iodobenzene diacetate and iodine, provided the azonane **205** as a single isomer in 72% yield *via* a radical-fragmentation-oxidation reaction (Scheme 4.81) [83].

Insertion of a nitrogen atom could also be realized by classical Beckmann rearrangement (Scheme 4.82) [84]

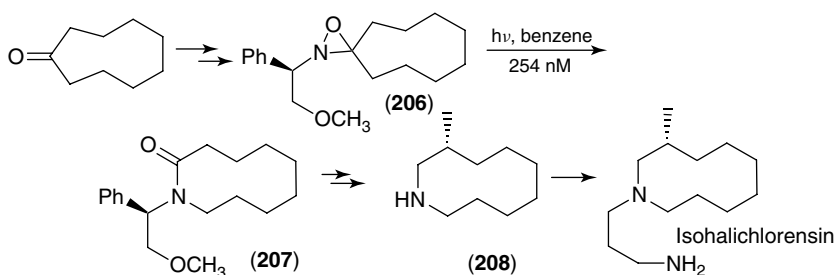
Applied to a more-membered ring, the photoinduced Beckmann ring expansion allowed, for example, the synthesis of the 10-membered framework of isohalichlorensins. Thus, photolysis at 254 nm in benzene of the chiral spirooxaziridine



**Scheme 4.81** Ring expansion of 4-hydroxyindoles.



**Scheme 4.82** Nine-membered ring lactam by Beckmann rearrangement.

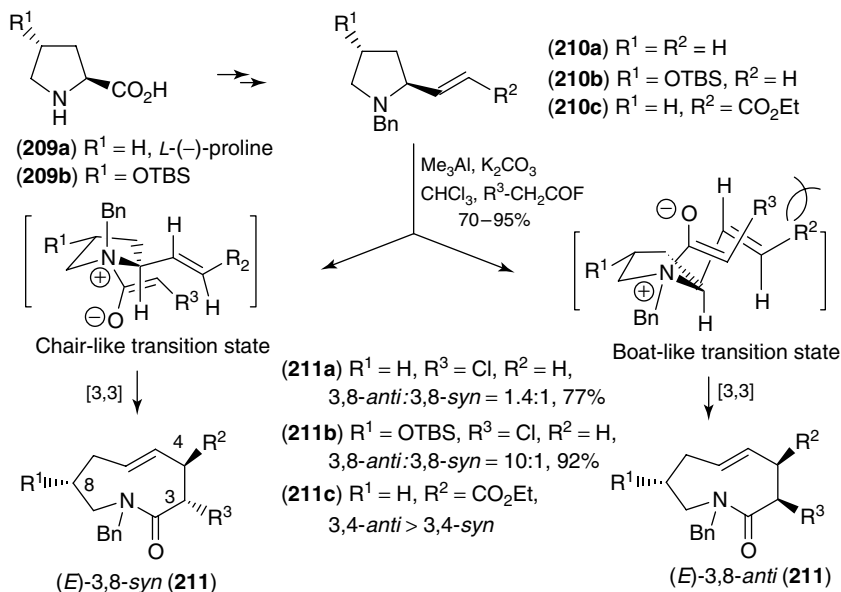


**Scheme 4.83** Enantioselective access to 10-membered amine.

**206** prepared from commercially available cyclononanone and (*R*)-(-)-1-amino-1-phenyl-2-methoxyethane, afforded the 10-membered lactam **207** in 57% yield, which could be further transformed in 54% yield to the (3*R*)-3-methylazacyclodecane **208**, precursor of the natural alkaloid isohalichlorensine (Scheme 4.83) [85].

Strained azocinones bearing an *E*-double bond within their skeletons are of particular interest because they constitute the key intermediates for the synthesis of diverse natural products. An original access to these compounds has been developed by zwitterionic aza-Claisen rearrangement of vinyl pyrrolidines with carboxylic acid fluorides [86]. This reaction led to enantiomerically pure azocinones with (i) exclusive generation of the *E*-double bond in the ring (ii) yields ranging 35–92% depending on the acid used (better yields were observed with phenylacetyl and chloroacetyl fluoride), and (iii) 3,4-*syn/anti* diastereoselectivity [86a] strongly influenced by the nature of the substituent ( $R^2$ ) in the starting vinyl pyrrolidine.

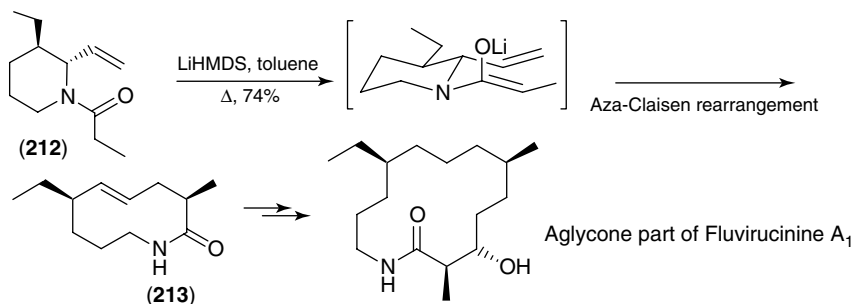
For example, unsubstituted vinyl pyrrolidine **210a** obtained from **209a** led to a mixture **211a** with almost no distereoselectivity. In contrast, when the bulky *tert*-butylsilyloxy (TBSO) group was used, 1,4-chirality transfer was nearly complete. Thus, pyrrolidine **210b**, easily prepared from *trans*-4-hydroxy-1-(-)-proline **209b**, reacted with various carboxylic acids ( $R^3 = \text{Cl}, \text{F}$ ) leading, after a Lewis acid activation of the resulting acyclic precursor followed by a base induced deprotonation of the acylimmonium salt, to a zwitterion which could exist in two transition states (TS), a chairlike and a boatlike TS. The final rearrangement proceeded then diastereoselectively *via* a preferred boatlike transition state affording predominantly (*anti/syn*: 10/1) the 3,4-*syn*-disubstituted (*E*)-azocinone **211b** with a *trans* relative configuration of the stereogenic centers C-3 and C-8 (Scheme 4.84) [86b].



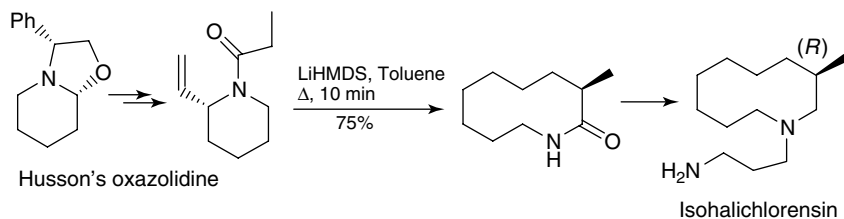
**Scheme 4.84** Aza-Claisen rearrangement of TBSO-substituted vinyl pyrrolidines.

*In contrario*, when the vinylic group of the pyrrolidine was substituted (**210c**) a change in the diastereoselectivity was observed and the 3,4-*anti* substituted azoninone **211c** arising from the preference for a chairlike transition state was majoritary formed as a result of the repulsive interactions between the substituent and the ester group detected in the boatlike transition state [86c].

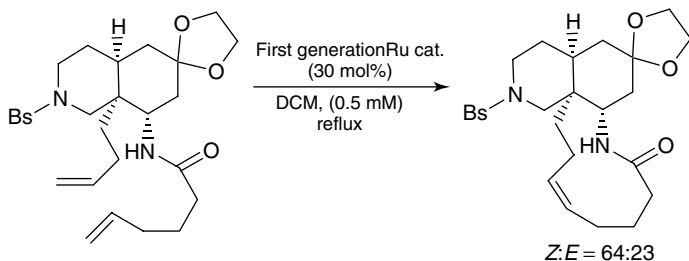
Enantioselective aza-Claisen rearrangement has been applied to the synthesis of 10-membered lactam starting from *trans*-2,3-disubstituted acyl piperidine **212**. The diastereoselectivity of this reaction induced by an amide enolate is due to (i) the favorable chair-chair like TS and (ii) the formation of the preferred amide (*Z*)-enolate. The lactam **213**, formed in 74% yield as the sole product, was further converted into the aglycone part of the macrolactam antibiotic fluvirucinine A<sub>1</sub> in 10 steps and 16% yield by standard transformations (Scheme 4.85) [87a].



**Scheme 4.85** Asymmetric aza-Claisen rearrangement.



**Scheme 4.86** Ring expansion to large-membered amine.



**Scheme 4.87** Formation of the C ring of Manzamine B by RCM reaction.

The same method, starting from (*R*)-*N*-propionyl-2-vinyl piperidine obtained from Husson's oxazolopiperidine, allowed also the synthesis of the 10-membered diamine isohalichlorensine [87b] (Scheme 4.86).

More recently, the applicability of the RCM reaction in the synthesis of medium-sized rings [34], which permits high yields and tolerates many functional groups, has been reported for the synthesis of 10-membered [88] and larger azacycles. For example, the 11 aza ring of manzamine B and the 15-membered azacycle of (+)-nakadamorin A were elaborated by this method (Scheme 4.87).

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## **Part Two**

# **Asymmetric Synthesis of Nitrogen Heterocycles With More Than One Heteroatom**



## 5

# Asymmetric Synthesis of Three- and Four-Membered Ring Heterocycles with More Than One Heteroatom

*Steve Lanners and Gilles Hanquet*

### 5.1

#### Introduction

Three- and four-membered N-containing heterocycles are invested with a special allure that is derived from their apparent simplicity and spartan architecture. Thus, these systems are multifaceted, and the literature continues to provide evidence of their diversity, both in terms of preparative routes and subsequent transformations. Among them, those containing two or more heteroatoms have, for the most part, only been synthesized in the second half of the twentieth century, even though some of them exhibit a synthetically useful balance between stability and reactivity. They are often used as versatile and selective reagents and in some cases, as synthetic intermediates or for their biological properties. While syntheses of such racemic small heterocycles have already been reviewed [1], only few papers were devoted to their stereoselective preparation.

This chapter highlights the stereoselective preparation of three- and four-membered N-heterocycles, both containing two or more heteroatoms, from the recent literature. We will generally focus on stereoselective transformations that lead to enantiomerically enriched N-heterocycles.

### 5.2

#### Three-Membered N-Heterocycles with Two Heteroatoms

Three-membered N-heterocycles with two heteroatoms were discovered only after 1950. A great number of them have been synthesized since then, using generally simple procedures familiar to synthetic chemists decades before. The saturated C–N–N rings (diaziridines) and their dehydrogenation products (diazirines) play the most important role in this field together with the C–N–O rings (oxaziridines). The latter are the most widely represented family in enantiomerically pure form as a result of their important applications in asymmetric synthesis [2]. Three-membered

N-heterocycles containing sulfur or phosphorus atoms are less common, because of their fewer applications and their difficult syntheses.

The stereochemistry of these small rings has received considerable attention mainly because of the chirality of the nitrogen atom and the generally appreciable barrier to its inversion (Equation 5.1) [3].



Enantioselective preparations of these small rings are mainly based on substrate-controlled diastereoselective ring construction starting from enantiomerically pure precursors. In many cases, this strategy is mainly based on nitrogen-heteroatom ring closure as depicted in Equation 5.2 [1e].



Some examples of photoisomerization of open chain 1,3 dipoles such as nitrones, azomethinimines and linear diazo compounds have also been employed but are less common.

### 5.2.1

#### Diaziridines

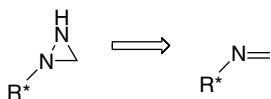
In general, the configuration at the nitrogen atom of trialkylamines ( $\text{NR}^1\text{R}^2\text{R}^3$ ) is invertible at room temperature, and they are impossible to isolate in optically active form. However, inversion of the N-atom in a three-membered ring system becomes remarkably slow [4]. The inversion barriers ( $108\text{--}113\text{ kJ mol}^{-1}$ ) have been determined by Mannschreck *et al.* in 1969 by means of NMR studies [5]. Generally, monocyclic diaziridines in solution and in the solid or gaseous state exist as 1,2-*trans*-isomers because the 1,2-*cis*-form is destabilized by n–n interactions of the nitrogen lone pairs and nonbonded interactions of N-substituents [6].

The first optically active diaziridines were reported in 1974 [7], and their absolute configurations were established by X-ray diffraction analysis. Chiroptical properties [8] and configurational stability were studied by racemization kinetics [9]. In 1979, Mannschreck *et al.* applied chiral chromatography to the optical resolution of diaziridines and also measured the inversion barriers by racemization kinetics [10]. In all known examples, the inversion barriers of diaziridines did not exceed  $117\text{ kJ mol}^{-1}$  and are related to the substitution pattern of the three-membered ring [2, 11].

Most enantiomerically pure diaziridines described in the literature result from optical resolution of a racemic mixture using chiral chromatography or crystallization [12]. Syntheses of racemic diaziridines almost always proceed by N–N bond

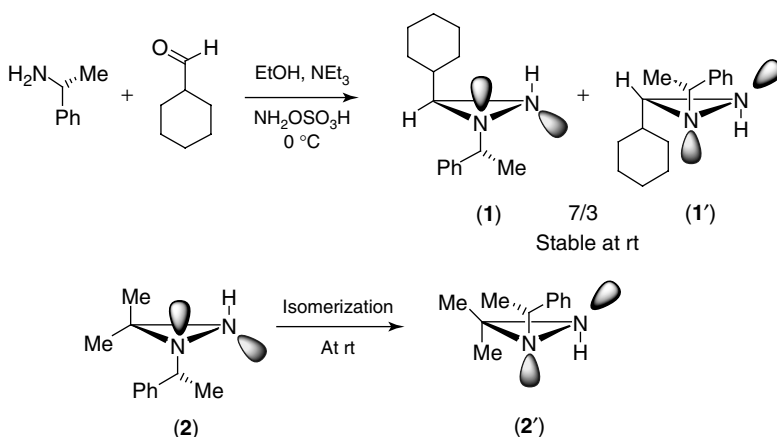
formation, using Schmitz's methodology, which consists of mixing an aldehyde or a ketone with an amine and an electrophilic amination agent [13]. The latter can be a chloramine, hydroxylamine-*O*-sulfonic acid (HOSA), or an *O*-sulfonylated hydroxylamine. As enantioselective electrophilic amination reagents remain unusual, the most interesting route to chiral nonracemic diaziridines is based on diastereoselective preparations starting from enantiomerically pure amines or ketones.

### 5.2.1.1 Substrate-Controlled Diastereoselective Diaziridination Using Chiral Enantiomerically Pure Amines



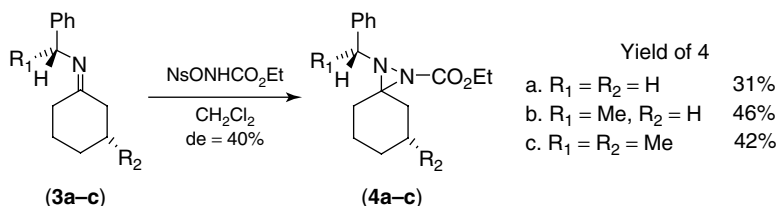
Ito *et al.* have studied the enantioselective N-atom transfer from chiral diaziridine **1** to  $\alpha,\beta$ -unsaturated amides leading to chiral aziridines with good diastereo- and enantioselection (ee 96%, *trans* maj.). Diaziridine **1** was prepared (under Schmitz's conditions) [13b] with (1*R*)-1-phenylethylamine from cyclohexanecarboxaldehyde as a mixture of two diastereomers **1**/**1'** (7:3) separable after column chromatography [14]. The configurations of **1** and **1'** were assigned by analogy to the diastereoselectivity reported for the preparation of **2**, bearing two methyl substituents on the endocyclic carbon, and its diastereoisomer **2'** [15]. While **2** gradually isomerized to its diastereoisomer at room temperature, **1** was found to be stable and could be used as enantioselective nitrogen-atom transfer reagent (Scheme 5.1). The presence of the *cis*-methyl group in **2** probably facilitates the isomerization.

Chiral nonracemic diaziridines have also been prepared from imines bearing chiral substituents on nitrogen using an [(arenesulfonyl)oxy]carbamate as aminating agent (Scheme 5.2) [16].



Scheme 5.1

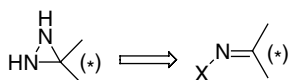




Scheme 5.2

The yields were modest but the diastereoisomeric mixtures of **4b** and **4c** are easily separated by flash chromatography and spirodiaziridines **4b** and **4c** were obtained as pure diastereoisomers.

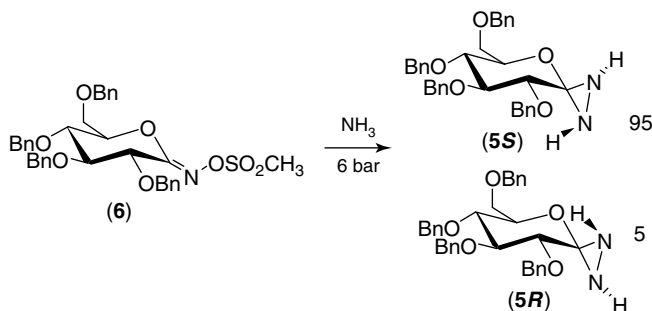
#### 5.2.1.2 Substrate-Controlled Diastereoselective Diaziridination Using Chiral Enantiomerically Pure Ketones



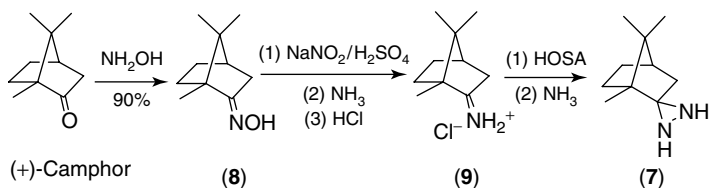
Vasella *et al.* have prepared glycosylidene diaziridines **5** as precursors of the corresponding diazirines [17]. The starting ketone was converted to (glycosylidene)amino sulfonate **6** [18] and finally treated with ammonia under pressure (Scheme 5.3). These diaziridines are mixtures of *trans*-configured diastereoisomers. The main (*S,S*)-configured isomer **5S** is stabilized by a weak intramolecular H-bond from *pseudoaxial* N–H to RO-C(2) [19].

This study suggests that the addition of the amine to lactone oxime sulfonate is kinetically controlled.

Vasella *et al.* showed later that the Schmitz conditions [13] could be applied directly on the corresponding ketone (validone) if a persilylated pyranoside nucleus was used [20]. The trimethylsilyl protecting group plays a crucial role for the formation of the diaziridine increasing the yields from 28% (for deprotected validone) [21] to 50%.



Scheme 5.3



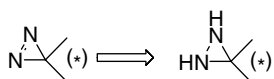
Scheme 5.4

2-Hydrazicamphane (7), which is also a precursor of the corresponding diazirine, was synthesized in enantiomerically pure form starting from (+)-camphor (Scheme 5.4) [22]. (+)-Camphor was converted to the corresponding oxime **8**, which after a nitrosation/rearrangement sequence followed by aminolysis afforded the imine hydrochloride **9** in good yields. Treatment of imine **9** with HOSA and  $\text{NH}_3$  delivered enantiomerically pure 2-hydrazicamphane **7**.

Schmitz's conditions [13b] have been applied to 14-hydroxydihydromorphinones to prepare the corresponding diaziridines with interesting opioid activity [23].

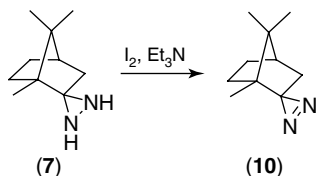
### 5.2.2

#### Diazirines



The recent emergence of diazirines as popular carbene precursors can be attributed to their relative stabilities with regard to acids, bases, and heat when compared with other sources [24]. The chiroptical properties of enantiomerically pure diazirines are of particular interest because the diazirine chromophore is very well suited for circular dichroism (CD) studies [25]. This was applied recently in studies dealing with the induced CD as a probe for structural analysis of supramolecular complexes [26]. Furthermore, the fact that diazirines are easily photoactivated by long-wave UV light makes them suitable for biochemical applications [27].

As diazirines are the dehydrogenation products of diaziridines, their synthesis is simple when the corresponding diaziridines are available. The preparation of 2-azicamphane **10**, which represents one of the very few examples of chiral enantiomerically pure diazirines, is performed by oxidation of 2-hydrazicamphane **7** (Scheme 5.5) [28].



Scheme 5.5

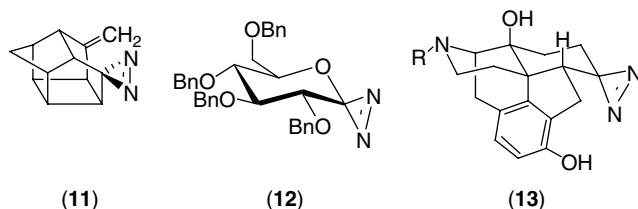


Fig. 5.1 Structures of diazirines 11, 12 and 13.

The chiral nonracemic diazirines 11 [29], 12 [17] and 13 [22] depicted in Figure 5.1 were also prepared by oxidation of the corresponding diaziridines.

### 5.2.3

#### Oxaziridines

The oxaziridines, three-membered rings containing nitrogen, oxygen, and carbon, have been of mechanistic and structural interest since their introduction in a classic paper by Emmons in 1957 [30]. This paper not only describes the preparation and structural proof of a new heterocycle but also contains the basis for most oxaziridine chemistry known so far, including rearrangement chemistry and decomposition of oxaziridines by low-valent metal salts [31]. During the following decade, oxaziridine chemistry remained confidential and this heterocycle became of interest for stereochemists in the 1970s because of the chirality of the nitrogen atom and the appreciable barrier to its inversion. This barrier to inversion was determined to be  $105\text{--}130\text{ kJ mol}^{-1}$  [32]. It turns out that the combination of placing a nitrogen in a three-membered ring (which destabilizes the  $120^\circ$  angle of the  $\text{sp}^2$ -like transition state involved in pyramidal inversion) with attaching the electron-withdrawing oxygen atom (which opposes the increased s-orbital character of nitrogen during inversion) makes simple oxaziridines the most interesting class of compounds containing a bona fide nitrogen stereogenic center [33]. Oxaziridines have also been shown to epimerize photochemically through a nitron intermediate [34].

While the inversion barrier is considerable in *N*-alkyl oxaziridines [35] and *N*-halogenated oxaziridines [36], it is smaller when the *N*-substituent is capable of  $\pi$ -conjugation (or hyperconjugation). *N*-aryl as well as *N*-acyl oxaziridines both have inversion barriers around  $90\text{ kJ mol}^{-1}$  [37, 38]. *N*-sulfonyl and *N*-phosphinoyl oxaziridines also exhibit a lower barrier to inversion as a result of hyperconjugation present in the system [39].

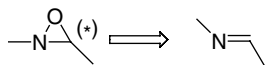
Synthetic applications of chiral oxaziridines concern photochemical rearrangement reactions affording chiral amides or lactams with high levels of enantio- or regioselectivity [40], and asymmetric heteroatom transfer reactions. Oxaziridines can be used as both electrophilic aminating and oxygenating agents in their reactions with a wide variety of nucleophiles. In spite of this dual reactivity, the predominance of one process over another can be affected by varying the substitution pattern on nitrogen. In general, oxaziridines with small groups on nitrogen (H, Me) [41, 42] or

aryl, acyl, carboxyamido [43], alkoxycarbonyl [44] groups act as aminating agents, whereas those with bulky [45] or strongly electron-withdrawing groups on nitrogen such as sulfonyl, sulfamyl, or phosphinoyl [46] groups preferentially transfer the oxygen atom [47]. Perfluoroalkyl oxaziridines [48] and oxaziridinium salts [49, 50] are highly reactive electrophilic oxygen-atom transfer reagents. The epoxidation of double bonds mediated by oxaziridinium salts are generally performed *in situ* via an organocatalytic process using the corresponding chiral iminium salts in substoichiometric amounts and Oxone as oxygen source [31, 51].

Enantioselective oxygen-atom transfer reactions onto nucleophiles, such as olefins, enolates or sulfides [52] represent the essential part of the applications of chiral oxaziridines in asymmetric synthesis. Chiral oxaziridines can be produced via oxidation of chiral nonracemic imines, oxidation of achiral imines with a chiral nonracemic peracid, via separation of diastereoisomeric oxaziridines produced from achiral peracid oxidation using chromatography [53] or enzymatic resolution [54]. A few resolutions of racemic oxaziridines using complexation or inclusion with chiral host complexes have also been reported [55]. Several nonoxidative methods have been also developed but are less general: photocyclization of nitrones carrying a chiral substituent and photocyclization of achiral nitrones in an optically active environment. Finally, derivatization at the nitrogen atom of chiral nonracemic stable N–H oxaziridines can therefore provide a useful alternative method to peracidic oxidation of chiral nonracemic imines, for the preparation of N-functionalized oxaziridines.

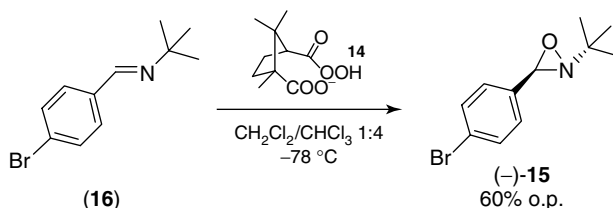
The electrophilic amination of ketones [13b] and the double 1,4 conjugate addition of hydroxamic acids to propiolates [56] to give racemic oxaziridines have been described but no asymmetric versions of these methods have been developed so far.

#### 5.2.3.1 Chiral Peracidic Oxidation of Achiral Imines



The first preparation of an oxaziridine, and still the most widespread method today, was the oxidation of an imine with a peracid. Rapidly, attempts to obtain enantiomerically enriched oxaziridines using chiral nonracemic peracids have been performed. The most commonly used oxidizing agent is (*S*)-(+)-peroxycamphoric acid (monoperoxycamphoric acid (MPCA) **14**) [57]. In most instances, the degree of asymmetric induction afforded by MPCA is rather low [35, 58]. Nevertheless, the use of crystalline MPCA at  $-78^{\circ}\text{C}$  in a carefully selected solvent system can give optical purities of up to 60% for oxaziridine **15** [59]. (Scheme 5.6)

Modest enantioselectivities (5–33% optical yield) have been observed when mixing different imines with *meta*-chloroperbenzoic acid (*m*-CPBA) in the presence of optically active carbinols [60]. The better selectivities were observed with chiral acyclic or aromatic trifluoromethyl-carbinols and are correlated with the reaction temperature and the relative amount of chiral solvent [61]. As one has to consider



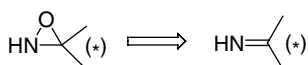
Scheme 5.6

that in the presence of chiral alcohols the peracid can be hydrogen-bonded to the solvent to produce a chiral peracid form, the authors proposed a chiral carbinol-imine solvation via hydrogen bonding between the imine nitrogen and the chiral protic solvent.

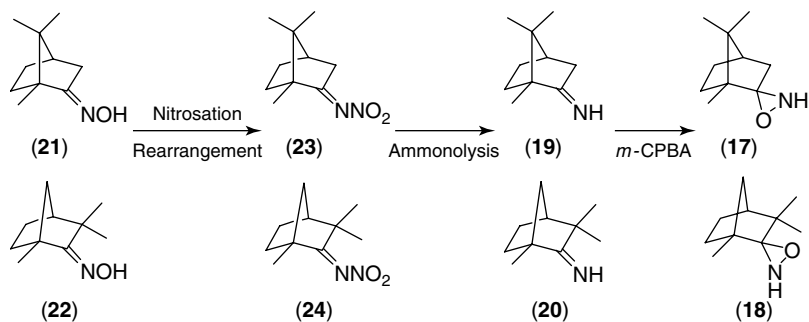
### 5.2.3.2 Achiral Peracidic Oxidation of Chiral Nonracemic Imines

Diastereoselection of substrate-controlled peracidic oxidations of chiral nonracemic imines is generally excellent. The mechanism of oxidation of imines has been studied and found to proceed through a two-step sequence, through cleavage of  $\pi$  bonding followed by the elimination of one molecule of carboxylic acid, rather than a concerted oxygen transfer [62–64]. This method is the most widely used for preparation of chiral oxaziridines of high optical purities, starting from enantiomerically pure imines. In the same manner as that in diaziridines, the stereogenic center of the imine can come either from the ketone or the amine part. In the latter case,  $\alpha$ -methylbenzylamine is widely used because of its low cost and ease of removal under dissolving metal conditions. This methodology will be illustrated by the most representative examples for each kind of N-substituted oxaziridines.

### N-Unsubstituted Oxaziridines



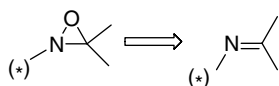
Although the first N–H oxaziridine was reported in the 1960s [65], because of their general instability, only a few N–H oxaziridines have been prepared and utilized for their ability to transfer an amino group to various nucleophiles [41, 66]. The preparation of the first stable enantiomerically pure chiral N–H oxaziridines has been accomplished only very recently by Page *et al.* [67]. These N–H oxaziridines 17 and 18, derived from (1*R*)-(+)-camphor and (1*R*)-(+)-fenchone were remarkably stable and used as asymmetric electrophilic nitrogen-atom transfer reagents on various ester- and nitrile-containing carbon nucleophiles [24]. Classical treatment of ketones with HOSA or a precursor of a chloramine to prepare N–H oxaziridines [13] were totally ineffective on camphor or fenchone. Thus, Page *et al.* decided to oxidize the primary (N–H) imines 19 and 20, which were prepared from the corresponding oximes 21 and 22 via the nitrimines 23 and 24, with *m*-CPBA (Scheme 5.7). The N–H oxaziridines 17 and 18 were obtained with good overall



Scheme 5.7

yields in enantiomerically pure form as diastereoisomeric mixture (6/4) at the pyramidal nitrogen atom. The diastereoisomers observed arise from the two configurations at the nitrogen atom resulting from *endo* attack of the oxidant on the imine **19** and *exo* attack of the oxidant on the imine **20**.

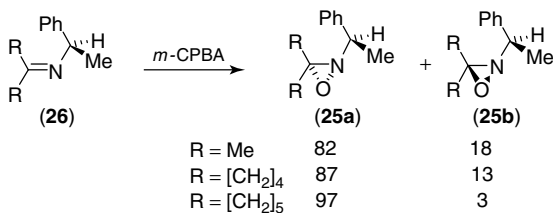
### N-Alkyl Oxaziridines



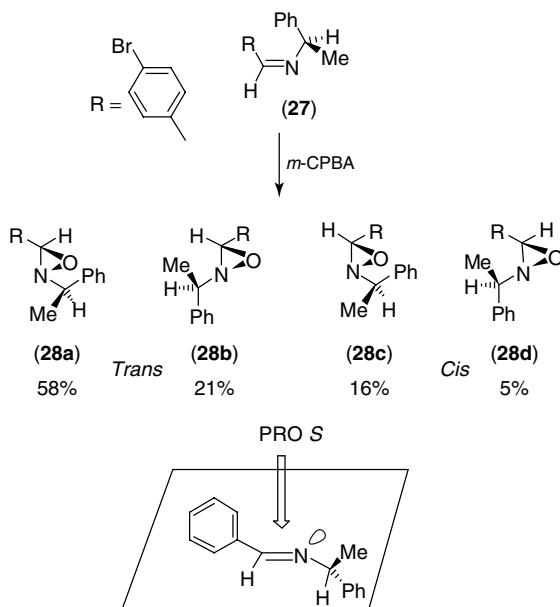
The pioneering work concerning diastereoselective peracidic oxidation of imines has been performed on Schiff bases [68] bearing a chiral substituent on nitrogen, namely, (*S*) or (*R*)- $\alpha$ -phenylethylamine. In the case of acyclic imines, the configuration of the C–N double bond influences the stereochemical outcome of the reaction. Using imines such as **26** derived from symmetrical ketones, a mixture of *N*-epimers **25a,b** is obtained (Scheme 5.8) [69].

When aldimines or imines derived from unsymmetrical ketones are employed, four oxaziridines are obtained [70]. A pro-*S* attack of the peracid is proposed to account for the observed absolute configurations of oxaziridines **28** (Scheme 5.9).

A stereospecific oxidation of chiral *trans*-aldimines leading to the corresponding (*E*)-oxaziridines has been described when a nitrile–hydrogen peroxide system was used as oxygen source instead of *m*-CPBA [71].



Scheme 5.8

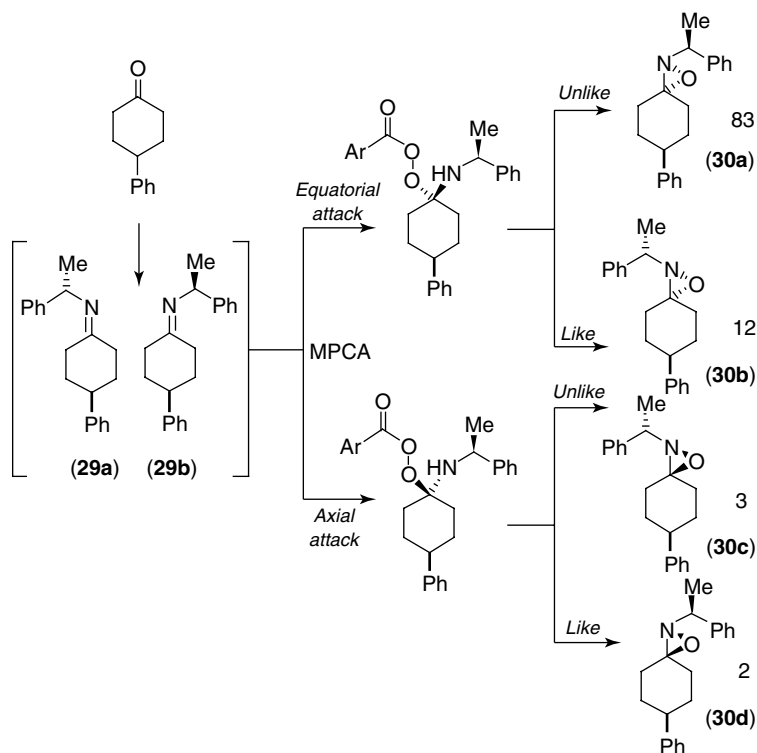


Scheme 5.9

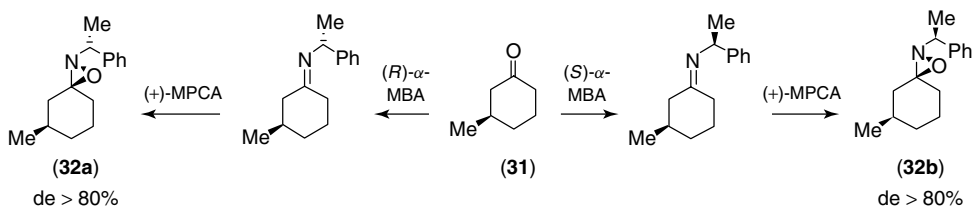
Chiral nonracemic spirocyclic oxaziridines are important compounds in stereoselective synthesis as a result of their possible stereospecific photorearrangement leading to chiral lactams [72]. Stereospecific cyclic expansion occurs generally in which the group *syn* to the chiral N-substituent of the oxaziridine undergoes preferential migration to nitrogen upon photolysis. By use of chiral nitrogen substituents (typically  $\alpha$ -methylbenzyl) on symmetrical cyclic imines, it is possible to control the absolute stereochemistry of the oxaziridine nitrogen atom [73]. Oxaziridines derived from six-membered cyclic imines tend to form via equatorial attack [74] and are also subject to control by a chiral group on nitrogen substituent (Scheme 5.10) [22].

Condensation of a 4-substituted cyclohexanone generates a mixture of diastereomeric imines **29a–b**. Addition of the peracid to either imine can afford products of equatorial attack or axial attack, with the former being favored. Finally, N–O bond closure occurs such that the newly generated nitrogen stereogenic center emerges preferentially with the *unlike* [75] relative configuration when  $\alpha$ -methylbenzylamine was used for imine formation. The selectivity toward the equatorial/*unlike* product increases as the bulkiness of the peracid and of the substituent of the cyclic imine become more important [76]. Imines prepared from cyclohexanones containing bulky substituents, presumably have a superior ability to prejudice the six-membered ring into one chairlike conformation over the other.

If a stereogenic center is located on the cyclohexane skeleton such as in the case of (*R*)-(+)-3-methylcyclohexanone **31**, the overall stereochemical control results from a matched effect between this stereogenic center and the benzylic stereocenter on the nitrogen [77]. (Scheme 5.11)



Scheme 5.10



Scheme 5.11

Condensation of (*R*)- $\alpha$ -methylbenzylamine and (*S*)- $\alpha$ -methylbenzylamine on (*R*)-(+)-3-methylcyclohexanone **31** followed by peracidic oxidation using (+)-MPCA delivers the oxaziridines **32a** and **32b** with an excellent diastereoselectivity. In each case, attack of the oxidizing agent takes place from an equatorial direction, leading to the *cis* relationship between the C-3 methyl group and the oxaziridine oxygen. In addition, oxidation affords products in which the benzylic stereogenic center and the oxaziridine nitrogen have *unlike* [75] relative stereochemistry [78]. (+)-MPCA is used only for its steric hindrance as any given stereocenter of this peracid is too far away from the forming bonds to have an effect on the face selectivity of the

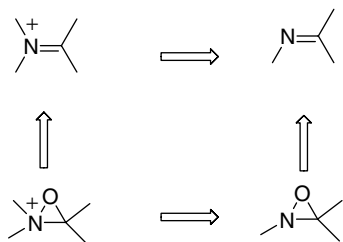


oxygen addition. Interestingly, photorearrangement of oxaziridines **32a–b** affords the corresponding regioisomeric lactams stereospecifically.

The peracid oxidation of imines derived from 2-alkyl-substituted cyclohexanones gives more complex mixtures because of partial epimerization at C-2 position during imine formation and oxidation of the enamine tautomer [79]. The stereoselection of the reaction drops dramatically leading to a number of very minor oxaziridines accompanying one or two major isomers in the reaction mixture [72].

The effect of polar substituents at the C-2 position on the stereoselectivity of oxaziridine formation [80] has also been recently studied on the same substrates [81]. In contrast, the general equatorial attack by *m*-CPBA observed onto 4- and 3-alkylsubstituted cyclohexylimines or 2-methoxy-substituted cyclohexylimines can be changed into axial attack for 2-hydroxylated cyclohexylimines in favorable circumstances. A *syn* hydroxyl-directed approach of the peracid in the same manner as *syn*-directed epoxidation of allylic alcohols is proposed to take into account this unusual stereoselectivity.

#### N-Alkyl Oxaziridines as Precursors of N-Quaternarized Oxaziridines



N-alkyl oxaziridines are sluggish for epoxidation of alkenes and even for sulfoxidations but quaternarization of their nitrogen atom significantly enhances the oxygen transfer reactivity [49, 50]. N-Alkylation leads to oxaziridinium salts that are among the most efficient agents for oxygen transfer onto nucleophilic substrates. It has also been demonstrated that oxygen-atom transfer from N-alkyl oxaziridines could be promoted by Brønsted or Lewis acids [82, 83].

Since the first report of steroidal oxaziridinium salt **33** by Lusinchi and coworkers in 1976 [84] and the establishment that such N-quaternarized oxaziridines are powerful electrophilic reagents for oxyfunctionalization of organic substrates [49, 50], their potential as asymmetric epoxidating agents has been intensively pursued (Figure 5.2) [85].

Chiral nonracemic oxaziridinium salts are generally generated *in situ* by peracidic oxidation of the corresponding enantiomerically pure iminium salts which are used for epoxidations in substoichiometric amounts in a catalytic cycle [50, 51, 85].

Only few optically active oxaziridinium salts have been isolated so far and most of them result from N-methylation of the corresponding enantiomerically pure oxaziridines. This alkylation reaction does not affect the configuration of the three-membered ring. The peracidic oxidation of iminium salts also leads to optically active oxaziridinium salts, but generally their isolation via this pathway is

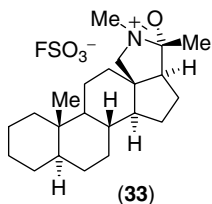
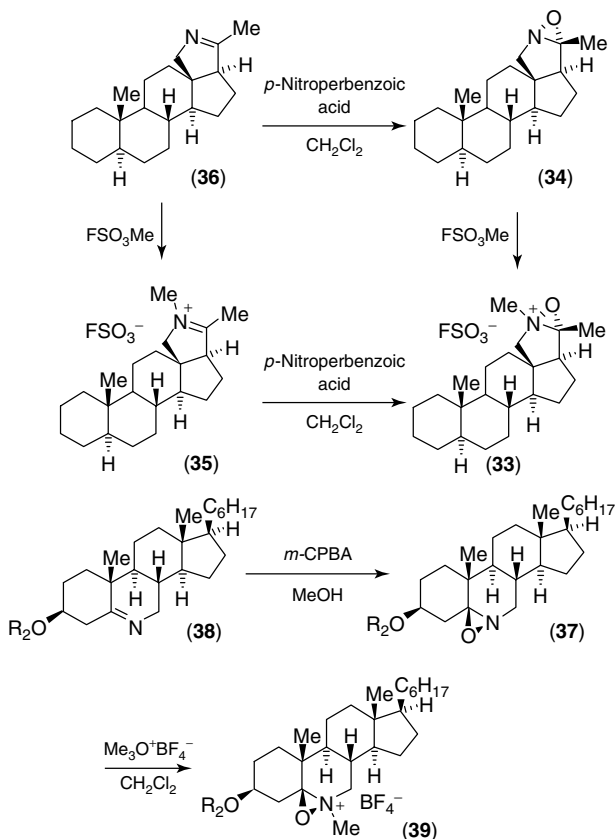


Fig. 5.2 Structure of the first isolated oxaziridinium salt.

more difficult. We only focus on the preparation of oxaziridinium salts that have been isolated or clearly detected in solution.

**Steroid-Based N-alkyl Oxaziridines** Enantiomerically pure steroid-based oxaziridines **34** [86] and **37** [87] have been obtained by a stereoselective peracid oxidation of the corresponding imines **36** and **38**. A total selectivity of the peracid attack for the  $\alpha$  face of **36** and the  $\beta$  face of **38** was observed (Scheme 5.12). Peracidic oxidation of



Scheme 5.12

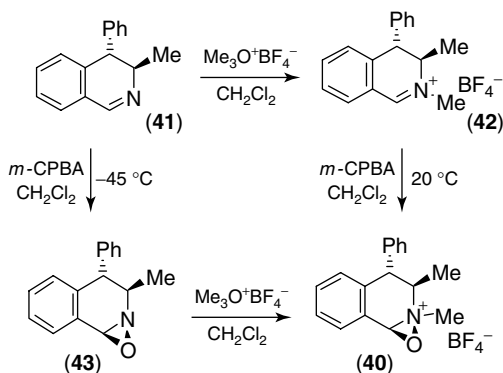
iminium salt **35** afforded oxaziridinium salt **33** with the same complete  $\alpha$ -selectivity [84]. Oxaziridine **34** can also be prepared by treatment of the corresponding nitron by *p*-tolylsulfonyl chloride in basic medium [88]. Oxaziridinium salts **33** and **39** result from methylation of the corresponding enantiomerically pure oxaziridines **34** and **37**.

**Dihydroisoquinoline-based N-alkyl oxaziridines** In 1993, the enantiomerically pure oxaziridinium salt **40** was isolated by crystallization and fully characterized including X-ray diffraction [89, 90]. It was conveniently prepared from benzaldehyde and (1*S*, 2*R*)-(+)-norephedrine via enantiomerically pure dihydroisoquinoline **41** following two possible stereoselective pathways already described for oxaziridinium **33** (Scheme 5.13).

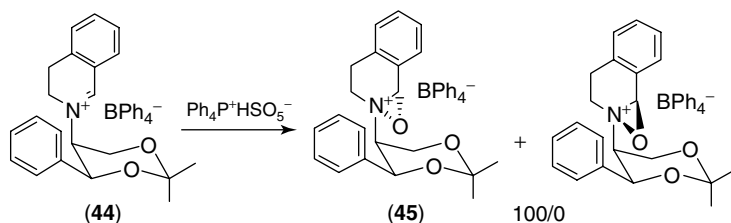
While the peracidic oxidation of the iminium **42** was fully stereoselective at room temperature, that of the parent imine **41** had to be performed at low temperature ( $-45\text{ }^{\circ}\text{C}$ ) [82b, 91]. At room temperature, the peracidic oxidation of the dihydroisoquinoline **41** was not stereoselective and even not chemoselective as the corresponding nitron was detected as side product. The *cis* relative configuration observed between the oxygen of the oxaziridine ring and the methyl substituent of oxaziridine **43** and oxaziridinium **40** can result from minimization of torsional strain during the formation of the three-membered ring [92].

Catalytic asymmetric epoxidations mediated by the dihydroisoquinolinium salt **44** derived from a chiral amine delivered good level of enantioselectivity for various olefins [93]. Nonaqueous conditions developed by Page *et al.* have allowed NMR spectroscopy to be carried out on the reaction mixture and show the stereoselective formation of the corresponding oxaziridinium salt **45** (Scheme 5.14) [94].

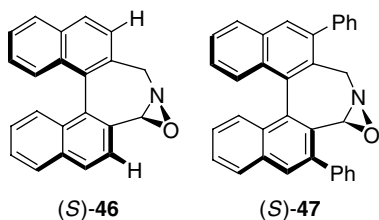
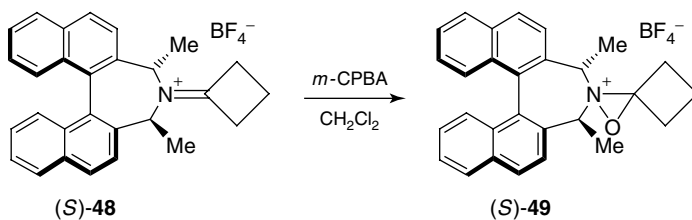
**Binaphthyl-based N-alkyl Oxaziridines** Recently, enantiomerically pure oxaziridines **46** and **47** have been prepared as acid-promoted asymmetric sulfoxidation reagents [95]. They resulted from a stereospecific oxidation of the corresponding enantiomerically pure imine by *m*-CPBA in methanol, leading to single enantiomers (Figure 5.3). The formation of the  $S_C$ ,  $R_N$  isomer can be interpreted as a result of a steric



Scheme 5.13



Scheme 5.14

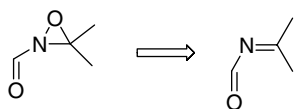
Fig. 5.3 Structures of oxaziridines **46** and **47**.

Scheme 5.15

repulsion between the arene hydrogen and an oxygen of the perester of the minor intermediate [92].

Binaphthyl-based iminium salt **48** with  $\text{C}_2$ -symmetry has been transformed by peracidic oxidation into the enantiomerically pure oxaziridinium salt **49** that has been clearly characterized in solution by NMR spectroscopy (Scheme 5.15). A dichloromethane solution of the oxaziridinium salt **49** was used at low temperature to epoxidize various olefins with enantioselectivities up to 75% [96].

### N-Acyl and N-Alkoxy carbonyl Oxaziridines



N-acyl and mostly N-alkoxy carbonyl oxaziridines have found extensive use as a source of electrophilic nitrogen [43, 97, 98]. An asymmetric variant of this methodology would be useful as the development of efficient chiral nonracemic

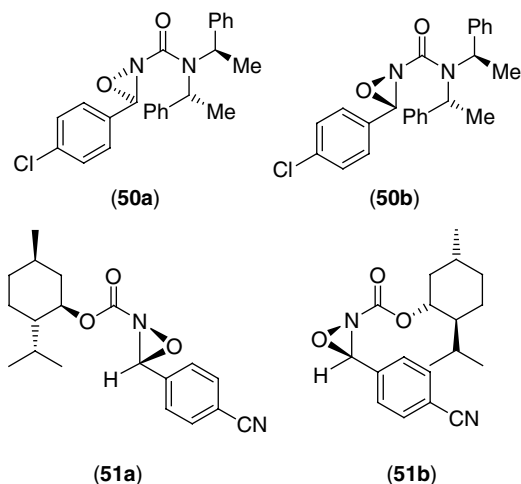


Fig. 5.4 Examples of chiral N-substituted oxaziridines.

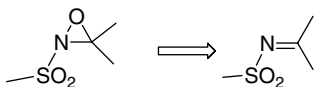
reagents for asymmetric transfer of electrophilic nitrogen to organic substrates is an important contemporary goal.

Only two chiral N-protected oxaziridines **50** [99] and **51** [100] have been prepared so far, both by the same group. The stereogenic center of the starting imines is located on the amine part for all of them (Figure 5.4).

N-Carboxamido oxaziridines **50** were prepared by biphasic basic *m*-CPBA oxidation of the corresponding N-carboxamidoimines as a mixture of two diastereoisomers which are *trans* isomers with opposite configuration at the ring carbon. They have been used as the first asymmetric sulfimidation reagents [82] of thioethers and aziridination reagents of olefins [101] giving interesting enantiomeric excesses.

N-Alkoxycarbonyl oxaziridines **51** were prepared using the *m*-CPBA/BuLi system [43] as oxidant. The compounds were single diastereoisomers at the ring carbon disclosing a high diastereoselectivity with respect to facial attack on the imine carbon. Asymmetric lithium enolate amination was performed with oxaziridines **51** with modest enantiomeric excesses [83].

### N-Sulfonyl Oxaziridines



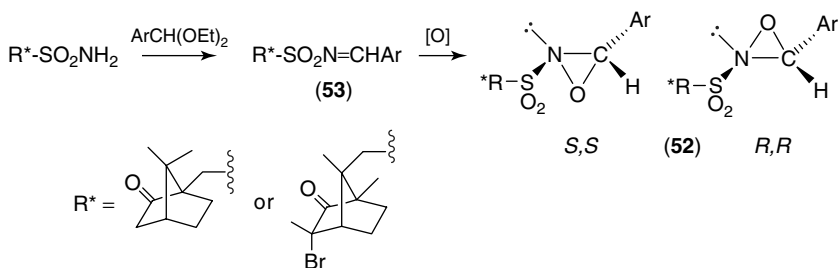
The development of reagents for the reagent-controlled asymmetric oxygen-atom transfer onto prochiral nucleophiles with high enantioselectivity is an important synthetic goal. To date, N-sulfonyl oxaziridines represent the most versatile and general active oxygen compounds able to oxidize many prochiral nucleophiles with high enantioselection [31, 47].

*N*-Sulfonyl oxaziridines **52** were the first examples of oxaziridines to have a substituent other than carbon or hydrogen attached to nitrogen. These stable oxaziridines are readily prepared by biphasic-buffered oxidation of chiral sulfonimines **53** with *m*-CPBA or potassium peroxymonosulfate [102]. The latter resulted from condensation of enantiomerically pure sulfonamides with the diethylacetal of an aromatic aldehyde. Since oxidation of sulfonimines give only (*E*)-2-sulfonyl oxaziridines [103], just two oxaziridine diastereoisomers having the *S,S* and *R,R* configurations at the three-membered ring are obtained upon oxidation of **53**. The best ratio of **52** (*S,S*/*R,R*) obtained reached 65/35 and was improved by fractional crystallizations to give optical yields (30–100%) depending on the nature of the aromatic substituent (Scheme 5.16) [104].

In order to increase the efficiencies of chiral 2-sulfonyl oxaziridines **52**, Davis *et al.* decided to vary the groups attached to the oxaziridine N and C atoms in a systematic manner. They found that chiral 2-sulfamyl oxaziridines **54** could be prepared by oxidation of the corresponding chiral 2-sulfamylimines, in enantiomerically pure form after separation of diastereoisomers by chromatography [105]. These oxaziridines were particularly efficient as enantioselective epoxidation reagents (ee up to 80%) when the aromatic substituent were perfluorinated (Figure 5.5).

3-Substituted 1,2-benzisothiazole-1,1-dioxide **55a–b** has been also developed as new *N*-sulfonyl oxaziridine [106]. It was obtained by biphasic oxidation of the corresponding imines in a 85/15 mixture of diastereoisomers. Several crystallizations from ethanol gave pure (+)-**55a** and (+)-**55b**, which were less effective than *N*-sulfamyl oxaziridines **54** in their asymmetric oxidations (Figure 5.6).

The camphor-derived oxaziridines **56–62** are of particular interest for two reasons: first, they are derived from materials readily available from the chiral pool with a rigid structure, thus reducing the problem of separation of isomers during the synthesis as observed for oxaziridines **52**, **54**, and **55**. Secondly, these oxaziridines



Scheme 5.16

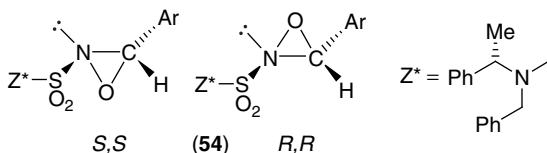


Fig. 5.5 Structure of *N*-sulfamyl oxaziridines **54**.

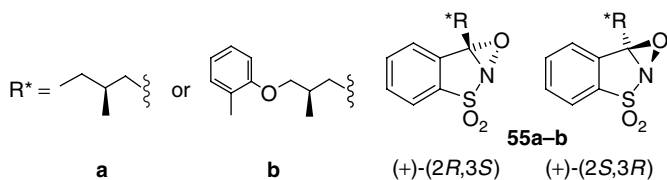


Fig. 5.6 Structure of N-sulfonyloxaziridines 55.

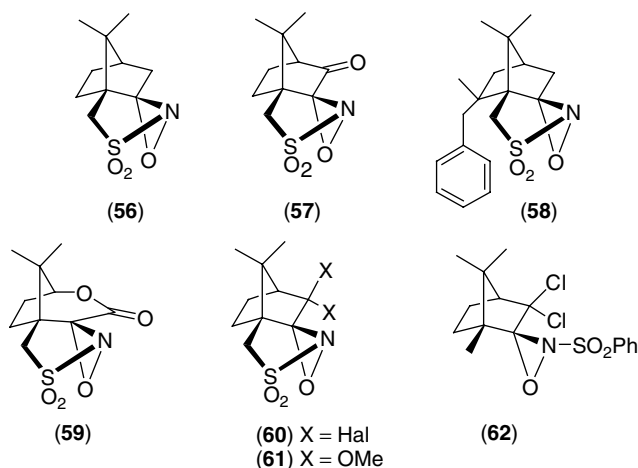
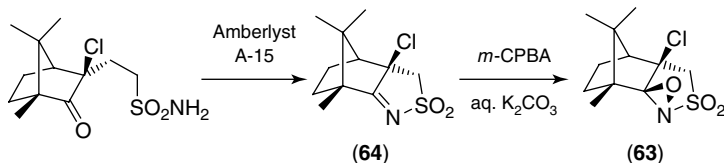


Fig. 5.7 Structure of camphoryl N-sulfonyloxaziridines.

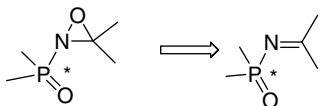
are among the most efficient reagents, specially **60** and **62**, for enantioselective sulfoxidations of thioethers and enantioselective  $\alpha$ -hydroxylation of carbonyl compounds. Not only is the product stereochemistry predictable, but the enantiomeric excesses often exceed 90% (Figure 5.7) [31, 47], [107, 108].

An important advantage of the camphorylsulfonyl oxaziridines is that upon oxidation of the corresponding imines, they are obtained as single isomers because the *exo* face of the C–N double bond is blocked by the methyl group of the methylene bridge.

Some *exo*-camphorylsulfonyl oxaziridines have been also described. For example, *exo*-oxaziridine **63** has been prepared by *m*-CPBA oxidation of camphor imines **64** [109]. This unexpected result is probably due to the conformation of the imine which prevents attack of the peracid from the *endo* direction (Scheme 5.17).



Scheme 5.17

**N-Phosphinoyl Oxaziridines**

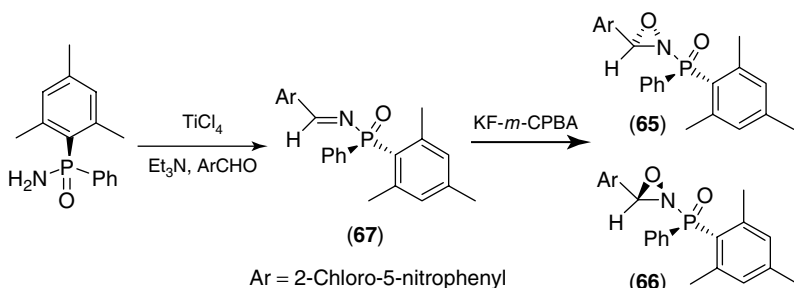
*N*-Phosphinoyl oxaziridines, like their better established *N*-sulfonyl analogs are generally prepared by peracidic oxidation of the corresponding imines [110]. Optically active *N*-phosphinoyl oxaziridines **65** and **66** containing a chiral phosphorus center have been prepared and evaluated as enantioselective oxygen-atom transfer reagents onto thioethers (Scheme 5.18) [111].

Oxidation of *N*-Phosphinoylimine **67** (75% ee) prepared from scalemic *R*-*P*-mesityl-*P*-phenylphosphinic amide (75% ee) with anhydrous *m*-CPBA/potassium fluoride complex [110] afforded a mixture of diastereoisomeric oxaziridines **65** and **66** (2.6:1) with total retention of the configuration at the phosphorus atom (75% ee).

**5.2.3.3 Photocyclization of Nitrones**

**Photocyclization of Achiral Nitrones in Optically Active Environment** Optically active oxaziridines can be obtained with generally modest enantioselectivity (optical purity 35%) by photoisomerization of achiral aldo- and keto-nitrones in the presence of a chiral solvent [112]. The best selectivities were obtained with (+)-(*S*) or (–)-(*R*)-2,2,2-trifluoro-1-phenylethanol [113]. More interesting is the irradiation of complexes of nitrones **68** and **69** in a crystalline inclusion with optically active (–)-1,6-di(*o*-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol that affords the corresponding oxaziridines with high enantioselectivity (>95% ee) (Figure 5.8) [114].

**Photocyclization of Chiral Nitrones** Photorearrangement of chiral nitrones to optically active oxaziridines has been found to occur in achiral solvents with optimum diastereoisomeric excess of 20% [113]. Because of low stereoselectivities observed, this method remained confidential.



Scheme 5.18



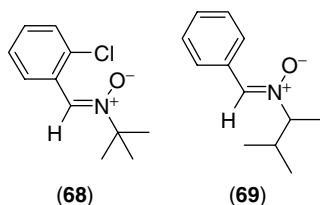


Fig. 5.8 Structure of nitrones **68** and **69**.

### 5.3

#### Four-Membered N-Heterocycles with Two Heteroatoms

Compared to the three-membered heterocycles mentioned above, their four-membered homologs give rise to a larger variety of structures as for each combination of heteroelements there are two possible constitutional isomers (i.e. the 1,2- and 1,3-di-X-cyclobutanes). In addition, a wide variety of synthetic methods, centered mostly around  $[2 + 2]$ -cycloadditions and similar processes have been developed for their synthesis, and have been comprehensively reviewed [1]. As previously, we only cover recent methods that stereoselectively access enantiomerically enriched heterocycles.

Despite their structural diversity, the four-membered N-heterocycles containing two (or more) heteroatoms have received much less attention than their smaller-ring congeners as far as their use as reagents or biologically active substrates is concerned. There are, however, a few notable exceptions. There is, for example, a fundamental interest in the electronic structure of some of the unsaturated four-membered ring structures in order to elucidate to what extent the presence of the heteroatoms renders these systems aromatic or antiaromatic [115, 116]. On the other hand, 1,2-diazetidines-3-ones, 1,3-diazetidines-2-ones (both often referred to as aza- $\beta$ -lactams), 1,2-thiazetidines-1,1-dioxides ( $\beta$ -sultams) and azaphosphetidines ( $\beta$ -phospholactams) have received more attention from the synthetic community as analogs of  $\beta$ -lactams and thus potential antibiotics [117]. Not surprisingly, more general strategies for the synthesis of the latter structures have been sought, but their asymmetric synthesis remains underdeveloped.

#### 5.3.1

##### Diazetidines

Diazetidines, the four-membered N-heterocycles, containing a second nitrogen atom comprise two isomeric types of structures, namely, 1,2-diazetidines **70** and 1,3-diazetidines **71** (Figure 5.9).

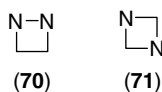


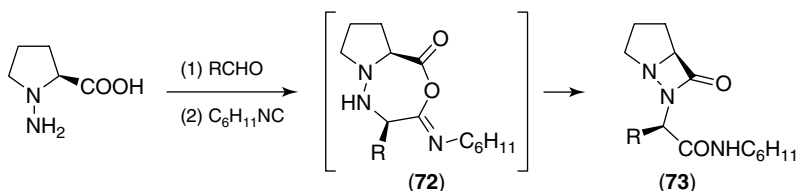
Fig. 5.9 General structures of diazetidine isomers.

Despite the fact that 1,2-diazetidines have been described as early as 1931 [118] and that the most general method for the construction of the more prominent aza- $\beta$ -lactams, namely, the reaction of azostilbenes with ketenes, dates back to 1941 [119], reports on chiral nonracemic diazetidines are scarce. Even the more recent and general strategies for the construction of these  $\beta$ -lactam analogs have not been developed to deliver enantiomerically enriched products [120].

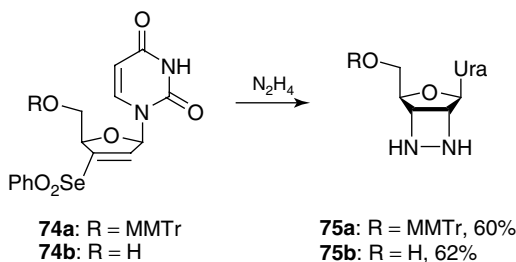
The first report concerning the synthesis of a scalemic 1,2-diazetidine-3-one was made in the context of the synthesis of dipeptides of L-proline with unnatural amino acids [121]. In an Ugi-type multicomponent reaction, *N*-amino-L-proline was reacted with an aldehyde and cyclohexylisocyanide to afford, presumably via the seven-membered intermediates **72**, the enantiomerically enriched diazetidines **73** in modest optical purities ranging from 22 to 35%. The latter were converted to the corresponding dipeptides by reductive cleavage of the N–N bond (Scheme 5.19).

More recently, a diastereoselective addition of hydrazine to the uridine-derived phenylselenones **74** was described as part of the synthesis effort toward nucleoside analogs [122]. 1,2-Diazetidines **75** were obtained in good yield as single diastereoisomers (Scheme 5.20).

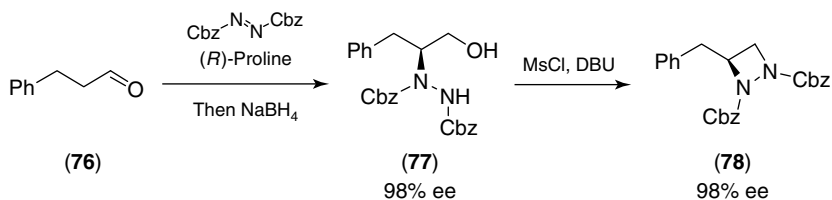
A simple procedure for the synthesis of chiral nonracemic 3-substituted 1,2-diazetidines has been published recently by Ma *et al.* [123]. The authors describe an approach based on the proline-catalyzed  $\alpha$ -hydrazination of aldehydes followed by aldehyde reduction and cyclization under Mitsunobu conditions or via the corresponding mesylate. Although most of their study was conducted with racemic proline, as a proof of principle 3-phenylpropanal **76** was reacted in the presence of (*R*)-proline and reduced *in situ* to afford 2-hydrazinoalcohol **77**, which was then cyclized to the diazetidine **78** in a one-pot procedure using methanesulfonyl



Scheme 5.19



Scheme 5.20



Scheme 5.21

chloride and DBU (Scheme 5.21). Both **77** and **78** were obtained with an excellent enantiomeric excess of 98%.

While these few methods are available for the synthesis of 1,2-diazetidines, their 1,3-isomers are even less studied. In particular, to our knowledge, there are no general methods described for the stereoselective synthesis of enantiomerically enriched 1,3-diazetidines. There are two reports on the synthesis of amino acid-derived diazetidinones by the reactions of tryptophan derivatives with alkyl isocyanates [124]; however, their structural assignments have later been questioned [125].

### 5.3.2

#### Oxazetidines

Oxazetidines are the four-membered heterocycles containing one nitrogen and one oxygen atom. As for their diazetidine counterparts, two possible constitutional isomers, i.e. the 1,2- **79** and 1,3-diazetidines **80**, are possible (Figure 5.10).

While the chemistry of these compounds has been comprehensively reviewed on several occasions [1], there are only scattered reports on their asymmetric synthesis – a characteristic they share with their diazetidine analogs (see Section 5.3.1). One might argue that the limited availability of stereoselective synthetic methods is due to the poor stability of many oxazetidines. However, the scarcity of target molecules containing the oxazetidine motif can also be regarded as a reason for the apparent lack of interest from the synthetic community.

Symptomatically, the isolation and first structural assignment of the halipeptins [126] – cyclic depsipeptides that were thought to contain a 1,2-oxazetidine moiety – immediately triggered studies toward the synthesis of this unusual fragment [127]. However, these studies only confirmed the structural revision that had been published in the meantime and supported the hypothesis that halipeptin contains a thiazole ring instead [128], an assumption that was later ascertained by total synthesis [129].

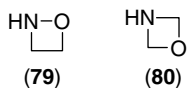
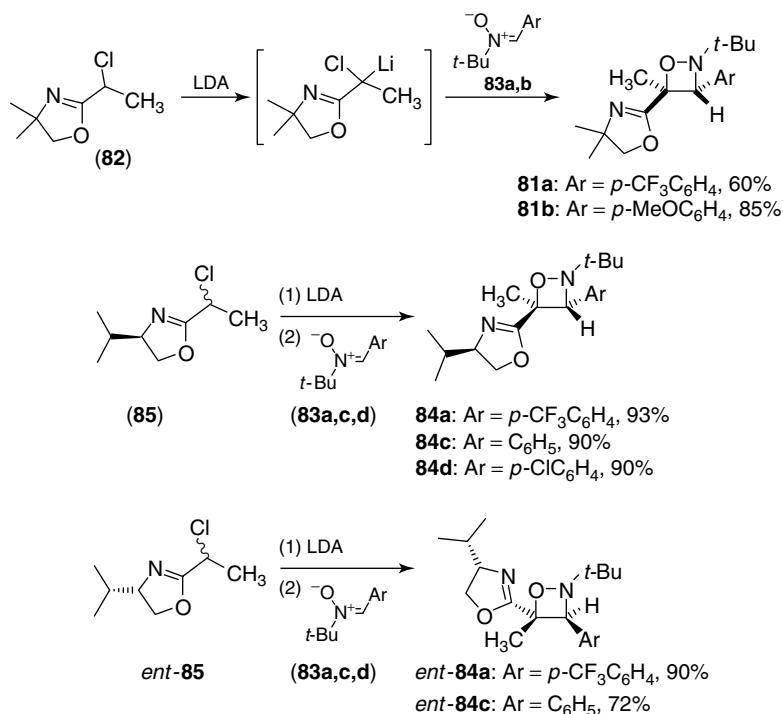


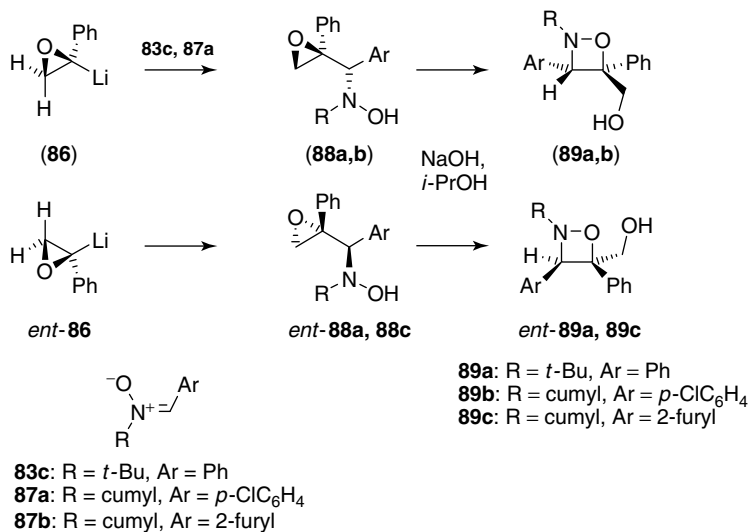
Fig. 5.10 General structures of oxazetidine isomers.

Recently, two methods for the synthesis of enantiomerically enriched 1,2-oxazetidines have been reported by Florio *et al.* Their interest in these structures arose when, during the course of studies aimed toward the synthesis of  $\alpha,\beta$ -unsaturated oxazolines, they discovered that 1,2-oxazetidines were formed during the reaction of  $\alpha$ -lithiated oxazolines with nitrones [130]. Careful optimization of the reaction conditions allowed the highly diastereoselective synthesis of 1,2-oxazetidines **81a,b** from readily accessible  $\alpha$ -chloro-oxazoline **82** via lithiation and addition to nitrones **83a,b** (Scheme 5.22) [131]. The reaction was found to be limited to the use of aromatic nitrones and enantiomerically pure oxazetidines **84a,c,d** and *ent*-**84a,c** could be obtained from the valinol-derived  $\alpha$ -chloro-oxazolines **85** and *ent*-**85**.

The same authors recently reported a similar synthesis of enantiomerically enriched oxazetidines on the basis of the diastereoselective addition of lithiated aryloxiranes to nitrones [132]. Having established the excellent diastereoselection of this process, they demonstrated its applicability to the synthesis of optically enriched substrates. Indeed, optically active oxiranyllithium reagents **86** and *ent*-**86** add to nitrones **83c** and **87a,b** to afford hydroxylamines **88a–c**, which upon treatment with NaOH in *i*-PrOH undergo an intramolecular epoxide opening to form oxazetidines **89a–c** with *er* of 98:2 (Scheme 5.23).



Scheme 5.22



Scheme 5.23

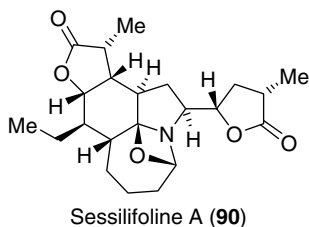


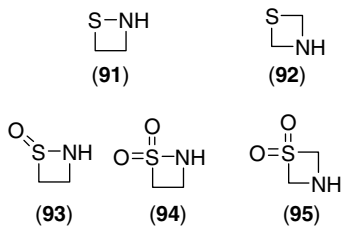
Fig. 5.11 Structure of sessilifoline A.

As was the case for 1,3-diazetidines, there are, to our knowledge, no methods described for the asymmetric synthesis of 1,3-oxazetidines. Again, it has to be emphasized that the strained bis-aminal functionality of these heterocycles makes them particularly reactive and unstable. However, the natural product sessilifoline A (**90**, Figure 5.11) was recently assigned a structure containing a 1,3-oxazetidine [133]. Hopefully, interesting natural product targets such as this one will rekindle the interest of the synthetic community in these rare heterocycles.

### 5.3.2.1 Thiazetidines

Thiazetidines are the four-membered heterocycles containing one nitrogen and one sulfur atom. Again, two types of constitutional isomers are possible: the 1,2- **91** and 1,3-thiazetidines **92** (Figure 5.12). In addition, the sulfur atom may be oxidized, and thus give rise to thiazetidine-1-oxides **93** and thiazetidine-1,1-dioxides **94**, **95**.

The chemistry of this family of heterocycles has been comprehensively reviewed [1]. Again, our focus will be on the stereoselective synthesis of enantiomerically enriched products, and in this area there are, to our knowledge no reports concerning compound types **91**, **92**, **93** and **94**. As suggested for the oxazetidines



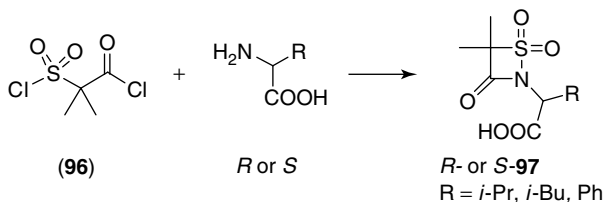
**Fig. 5.12** General structures of thiazetidines.

(*vide supra*), one might argue that it is the lack of attractive target structures that has prevented a more vivid interest in these structurally intriguing compounds. On the other hand, 1,2-thiazetidine-1,1-dioxides ( $\beta$ -sultams) of general structure **94** have received far more attention. We have mentioned the fundamental interest in the latter as more reactive analogs of  $\beta$ -lactam antibiotics [117]. This has been the main motivation of synthetic chemists to successfully develop approaches for their stereoselective preparation. In the following, we will distinguish between chiral  $\beta$ -sultams bearing stereogenic elements within or outside the four-membered ring and subdivide the synthetic methods accordingly.

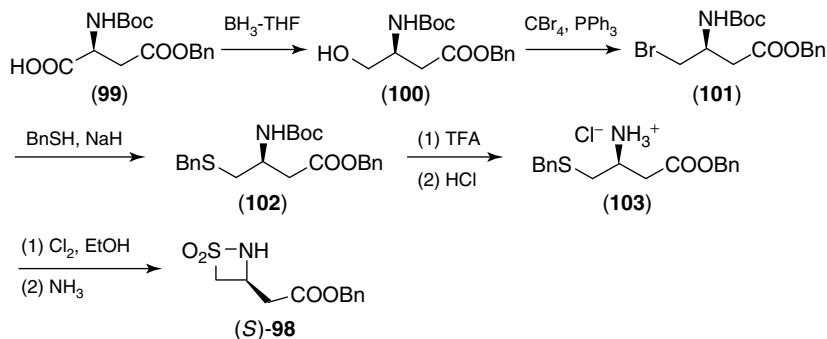
A simple and general synthesis of enantiomerically pure chiral  $\beta$ -sultams has been reported recently by Page *et al.* [134]. They report the reaction of (chlorosulfonyl)dimethylacetyl chloride **96** with a series of amino acids to afford the corresponding enantiomerically enriched  $\beta$ -sultams **97** (Scheme 5.24).

Otto *et al.* have recently described the synthesis of  $\beta$ -sultams bearing stereogenic centers on and outside the four-membered ring. While their first approach used only racemic  $\beta$ -sultam **98** that was derivatized on nitrogen by the use of chiral acid chlorides and on the carboxylate end with amino acids [135], they later developed an asymmetric approach to the same types of compounds (Scheme 5.25) [136]. Starting from orthogonally protected aspartic acid **99**, chemoselective reduction of the carboxylate group afforded amino alcohol **100**. The latter was transformed into bromide **101** and nucleophilic displacement produced sulfide **102**. The hydrochloride **103** was obtained after Boc deprotection, and was cyclized to (*S*)-**98** via a one-pot oxidative chlorination-base induced ring-closure sequence.

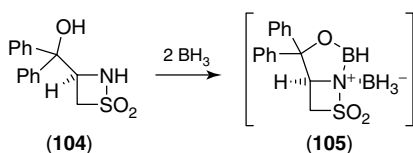
Several other examples of cyclization strategies starting from amino acids have been reported [137]. In particular,  $\beta$ -sultam **104**, obtained from (*R*)-cysteine, has been used to prepare oxazaborolidine catalyst **105** *in situ* by reaction with borane (Scheme 5.26) [138]. The latter was able to promote the enantioselective reduction



Scheme 5.24



Scheme 5.25



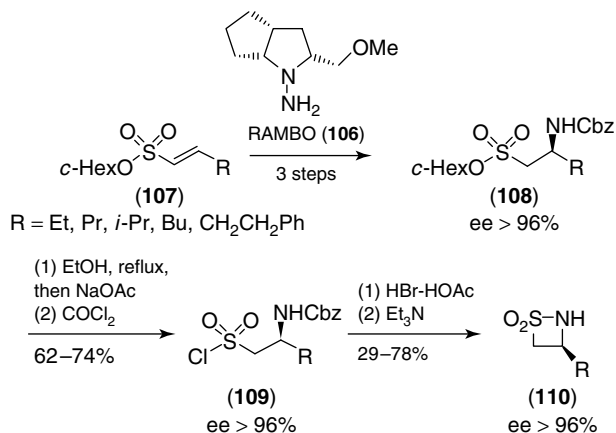
Scheme 5.26

of acetophenone with a good enantiomeric excess (81%), even though the reaction was run at an unusually high temperature ( $66^\circ\text{C}$ ).

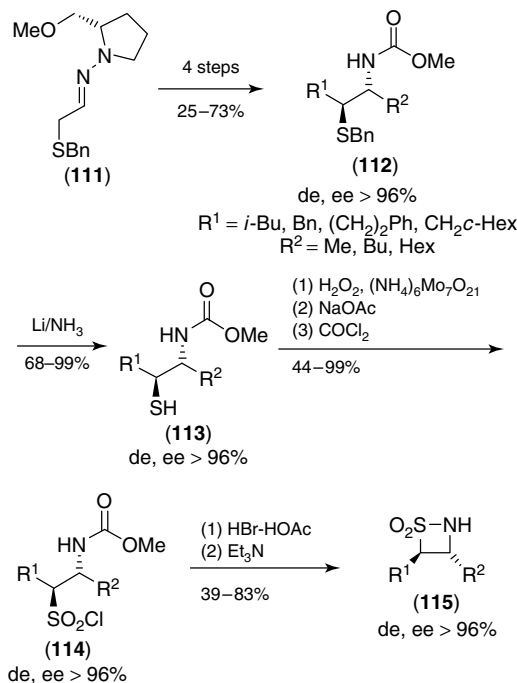
The same ring closure of open-chain  $\beta$ -amino sulfonates featured in the previous examples has also been put to profit by the Enders group. Their efforts in this area were initially seen as an extension of the conjugate addition methodology of chiral amines to  $\alpha,\beta$ -unsaturated sulfonates that had been developed in order to prepare taurine derivatives [139]. The best results were obtained with the RAMBO chiral hydrazine **106**, which was used in a three-step sequence involving Lewis acid-catalyzed conjugate addition to sulfonates **107**, followed by N–N bond cleavage and Cbz protection to afford  $\beta$ -amino sulfonates **108** with enantiomeric excesses in excess of 96% (Scheme 5.27) [140]. Subsequent sulfonate hydrolysis and chlorination afforded sulfonyl chlorides **109**. Cbz removal and base-induced cyclization afforded the desired  $\beta$ -sultams **110** that displayed no erosion of enantiomeric purity.

In a second approach by the Enders group, 3,4-disubstituted  $\beta$ -sultams were targeted, and the general strategy modified in order to include a diastereoselective alkylation of SAMP-hydrazone **111** [141]. The latter was transformed into  $\beta$ -amino sulfide **112** by a known sequence. Removal of the benzyl group afforded **113**, which was oxidized and chlorinated to obtain **114** (Scheme 5.28). The same deprotection and cyclization conditions used previously finished the synthesis of the *cis*-3,4-disubstituted  $\beta$ -sultams **115**.

An interesting synthesis of  $\beta$ -sultams, on the basis of a ring opening–ring closing strategy starting from isoxazolidines **116**, was recently described by Caddick *et al.* [142]. Although this strategy has been applied successfully to the diastereoselective



Scheme 5.27

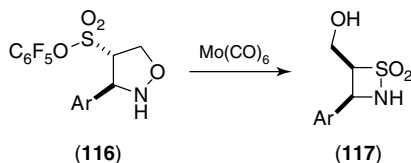


Scheme 5.28

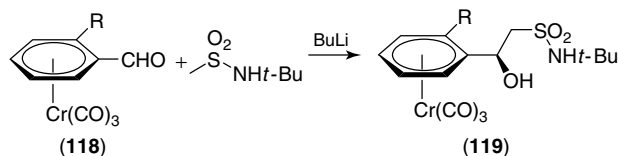
synthesis of the sultams 117 bearing a large variety of aryl substituents, no asymmetric version is available yet (Scheme 5.29).

All the previously described methods proceed by cyclization involving S–N bond formation. There is only one example of a stereoselective synthesis of  $\beta$ -sultams by a C–N bond formation. Del Buttero *et al.* used chiral (tricarboxyl)chromium arene

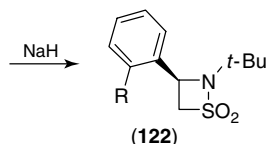
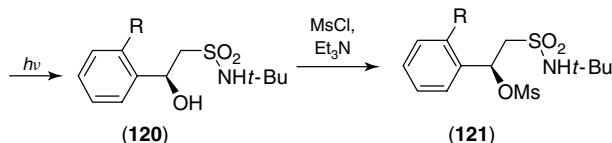




Scheme 5.29



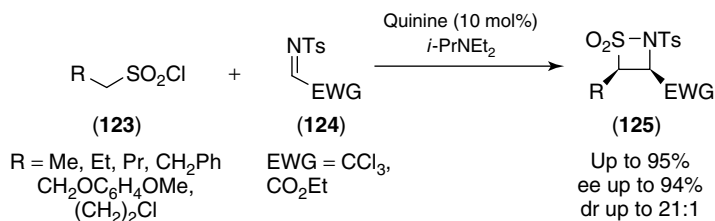
R = Me, OMe, Cl



Scheme 5.30

complexes **118** as starting point for their approach (Scheme 5.30) [143]. Diastereoselective addition of the dianion of *tert*-butyl methanesulfonamide afforded alcohols **119**, which were deprotected under photochemical conditions and the resulting alcohols **120** transformed into their corresponding mesylates **121**. Deprotonation of the sulfonamide nitrogen by  $\text{NaH}$  effected the intramolecular  $\text{S}_\text{N}2$  ring closure to afford  $\beta$ -sultams **122**.

Another appealing strategy for the formation of  $\beta$ -sultams is the  $[2 + 2]$  cycloaddition of sulfenes with imines. Despite the fact that this type of methodology had been known for several years [144], and that attempts at diastereoselective versions had been reported in solution [145] and on solid phase [146] with moderate success, there was no general asymmetric version available until the recent report by the Peters group [147]. A variety of sulfonyl chlorides **123** were used as sulfene precursors and reacted with electron-poor imines **124** in the presence of quinine as chiral catalyst. *cis*- $\beta$ -Sultams **125** were obtained in good yields and diastereo- and enantioselectivities (Scheme 5.31).



Scheme 5.31

## 5.4

### Conclusions

As illustrated above, three- and four-membered N-heterocycles with two heteroatoms are prepared by a wide variety of synthetic methods. There are several methods to synthesize certain ring systems in enantiomerically enriched form and, in many cases, as a result of its high inversion barrier, their nitrogen atom is stereogenic. Whereas the three-membered rings, and mainly enantiomerically pure oxaziridines, have been used as chiral substrates or chiral reagents in a variety of unique stereoselective transformations, their four-membered congeners, such as  $\beta$ -sultams, have been mainly prepared for their potential biological applications. Despite these diverse applications and the efforts outlined above, the enantioselective synthesis of these heterocycles remains underdeveloped. Especially in the area of the hetero-azetidines, many subclasses lack preparative methods of general scope, and certain constitutional isomers have never been synthesized asymmetrically. Undoubtedly, because of their growing interest, the chemistry of three- and four-membered N-heterocycles will provide synthetic challenges for some time to come.

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## 6

### Asymmetric Synthesis of Five-Membered Ring Heterocycles with More Than One Heteroatom

*Catherine Kadouri-Puchot and Claude Agami*

Asymmetric syntheses of chiral five-membered heterocycles containing two heteroatoms, one of which being nitrogen, have been the subject of several studies. Such compounds indeed are of manifold significance. First, they are intrinsically interesting owing to their various biological properties: anti-inflammatory ability ( $\Delta^2$ -pyrazolines), antibacterial activity (oxazolidinones and pyrazolidinones), ligands for dopamine receptors and platelet glycoprotein antagonists (isoxazolines), and anti-inflammatory drugs (thiazolines) can be quoted as very fragmentary examples.

In the second place, these heterocycles are extraordinary and useful reagents for the synthesis of a great variety of optically active molecules and most of them are the basis of new methodologies that are now widely used. In this context, many distinguished chemists have linked their names to processes that embody exceptional versatility in building elaborate optically active molecules often obtained in an enantiopure form.

Last but not least, many members of this family (especially, oxazolines and isoxazolines) are used as chiral ligands in metal-catalyzed enantioselective transformations; this property might appear as the most promising one and research in that direction is fast expanding.

Owing to these outstanding features, as can be expected, many reviews pertinent to this area are available and they will be cited in due course below. Therefore, the present review will focus on the more recent outcomes, and the most widely known results of the last 15 years will be described.

#### 6.1

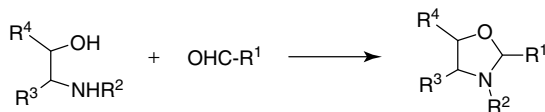
##### Five-Membered Heterocycles with N and O Atoms

###### 6.1.1

###### Oxazolidines

Chiral oxazolidines may be viewed as masked forms of aldehydes, and as such are widely employed as chiral auxiliaries in asymmetric synthesis. Since the





Scheme 6.1

stereoselective construction of this type of five-membered heterocycle is especially straightforward, this property has allowed numerous applications [1].

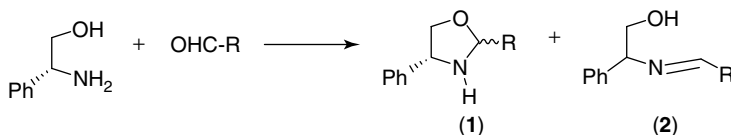
Basically, oxazolidines are easily formed by an acid-catalyzed reaction between an aldehyde (or an acetal) and a suitable 1,2-amino alcohol derived from an  $\alpha$ -amino acid or belonging to the ephedrine family (Scheme 6.1).

This transformation involves the prior formation of an iminium ion, which undergoes an intramolecular nucleophilic addition from the hydroxy group. This cyclization, which is the main pathway leading to such heterocycles [2], is nevertheless a disfavored 5-endo-trig process [3], and is unmanageable in the case of an unsubstituted amino group ( $R^2 = H$  in Scheme 6.1) reacting with aromatic aldehydes. Actually, in that case, the condensation (Scheme 6.2  $R = Ar$ ) leads to a mixture of the oxazolidine **1** (as an epimeric mixture) and its tautomeric hydroxyimine **2**, the ratio between them being dependent on many experimental features [4]; however, oxazolidine is always produced as the minor tautomer in this case. When the aldehyde is not an aromatic one, the imine tautomer **2** ( $R \neq Ar$ ) appears as a trace product but the created oxazolidine still appears as two epimers in nearly equal amounts. On the other hand, the fact that the cyclization goes to completion with all N-substituted amino alcohols (Scheme 6.1) can be viewed as a consequence of the classical Thorpe–Ingold effect.

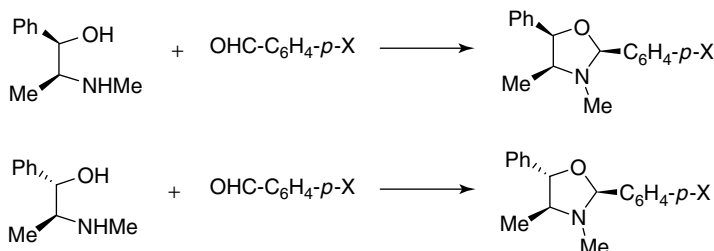
As stated above, the case of oxazolidine formation from N-substituted amino alcohol does not show any of these inconveniences: yields and stereoselectivities are excellent. However, the formation of N-alkyloxazolidines has to be treated separately from that of N-tosyl and N-Boc oxazolidines.

#### 6.1.1.1 N-Alkyloxazolidines

Considerable confusion about the structure of these heterocycles prevailed in the early stages, since an X-ray analysis published in 1971 [5] specified that condensation of ephedrine and *p*-bromobenzaldehyde led to a 2,4-*trans*-oxazolidine configuration. Many subsequent works [6, 7] have contributed to correct this assertion; it is now unambiguously established that, in all cases, the major oxazolidine isomer shows a relative 2,4-*cis*-configuration (the single crystal studied by Neelakantan [5] should not be representative of the dissolved material). Actually this *cis* configuration is



Scheme 6.2



Scheme 6.3

the result of a thermodynamic control and the less stable *trans* structure may, in some cases, appear solely as a transient species depending on the reaction medium [8]. Scheme 6.3 depicts two representative examples of oxazolidine formations from (–)-ephedrine [7] and from (+)-pseudoephedrine [8], respectively.

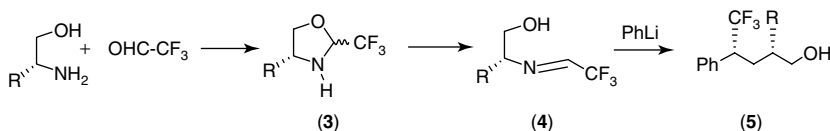
The fact that the 2,4-*cis* configuration is more stable than the *trans* one can be ascribed to the favorable *trans/trans* array between substituents on the C-2, N-3 and C-4 centers. This also explains why both C-2 epimers are equally stable when N-unsubstituted amino alcohols are involved.

The most used chiral amino alcohols are ephedrine [7, 9], pseudoephedrine [4], valinol [10], phenylglycinol [11], and their N-substituted derivatives. Recently [12], amino alcohols prepared from L-methionine and S-methyl-L-cysteine were employed for the synthesis of oxazolidines which were later used in the actively explored field [13] of asymmetric palladium-catalyzed allylations.

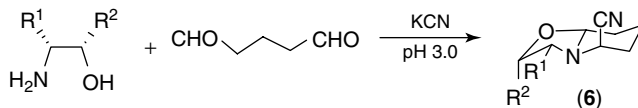
Oxazolidines are also valuable tools in the most challenging field of organofluorine compounds. A large array of amino alcohols was reacted with trifluoromethyl aldehyde, which afforded oxazolidines **3** in excellent yields but as an epimeric mixture (Scheme 6.4); this last fact is unimportant since these oxazolidines were transformed into their corresponding imine counterparts **4**, which exist as unique stereoisomers [14]. A highly diastereoselective organometallic addition to these imines affords the interesting chiral amino alcohols **5**.

Analogous trifluoromethyl-substituted oxazolidines also served as chiral auxiliaries for the alkylation of amides and for the synthesis of various  $\beta$ -amino acids,  $\beta$ -amino alcohols, and  $\gamma$ -amino alcohols via Reformatsky- and Mannich-type reactions [15]. Recently, it has been reported [16] that the oxazolidine formed from ephedrine and salicylaldehyde can be used as a catalytic ligand in the addition of diethylzinc to a variety of aldehydes.

An original methodology arose when a dialdehyde (namely glutaraldehyde) instead of an aldehyde was treated with phenylglycinol ( $R^1 = \text{C}_6\text{H}_5$ ,  $R^2 = \text{H}$ ) or



Scheme 6.4



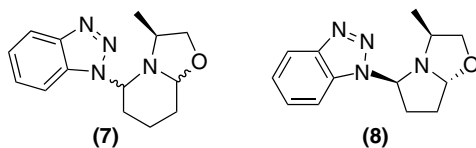
Scheme 6.5

norephedrine ( $R^1 = \text{CH}_3$ ,  $R^2 = \text{C}_6\text{H}_5$ ) as the amino alcohol counterpart, in the presence of potassium cyanide (Scheme 6.5); this led to the bicyclic oxazolidine **6** as a single isomer in which the classical 2,4-*cis* structure is still present (in that case, however, the favored *trans* junction of the bicyclic system should be taken into account to explain the stereoselectivity) [17a]. On the other hand, an anomeric effect explains the axial position of the cyano group, and this geometry is a crucial element for the numerous syntheses that were developed from this compound as starting material. This methodology, which permits the synthesis of many natural and unnatural derivatives containing either the piperidine or the pyrrolidine moieties, was dubbed the CN(*R*, *S*) method by its authors, Husson *et al.* [18].

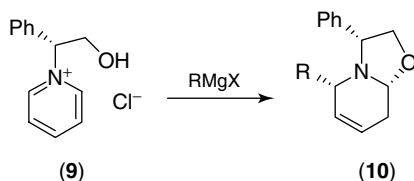
Some years after the preceding reports, Katritzky *et al.* described a similar condensation that also involves dialdehydes: glutaraldehyde [19a] and succinaldehyde [19b] which were made to react with phenylglycinol in the presence of benzotriazole (instead of potassium cyanide). Whereas the condensation product **7** formed from glutaraldehyde was obtained as a mixture of epimers and regioisomers [19c], this was not the case when succinaldehyde was the starting material; in this last case, the pyrrolidine homolog **8** was obtained as the single, more stable *trans* isomer (Scheme 6.6).

Another occurrence of this 2,4-*cis* structure in a bicyclic oxazolidine was found in the oxazolopiperidine **10**, which results from the highly stereoselective intramolecular cyclization (Scheme 6.7) of the pyridinium salt **9** [20].

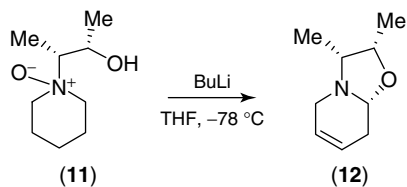
The cyclization depicted in Scheme 6.8 shows a cyclization that is related to the preceding one: oxazolidine **12** was synthesized from  $\beta$ -hydroxy tertiary amine *N*-oxides **11** [21]. Here again, the product shows the usual 2,4-*cis* geometry.



Scheme 6.6



Scheme 6.7



Scheme 6.8

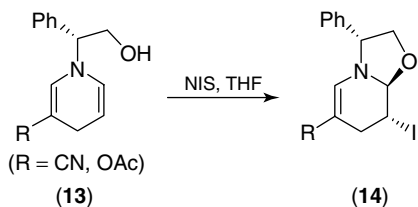
A moderate diastereoselectivity, favoring now the 2,4-*trans* geometry in compound 13, was reported during the iodocyclization of 1,4-dihydropyridines 14 [22]. It should be noted that an iminium ion does not come into play (as in the preceding reactions): cyclization occurs on an iodonium ion and the reaction product may not be thermodynamically controlled (Scheme 6.9).

Intermediate iminium ions are also involved during the partial reduction of  $\delta$ -lactams whose intramolecular cyclization (Scheme 6.10) leads oxazolopiperines. Thus, compound 16 was obtained from the readily available bicyclic lactam 15 and eventually cyclohexenone 17 was produced in >99% ee [23].

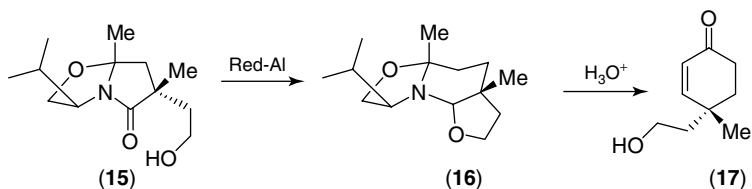
$\delta$ -Lactam 18 can be converted into oxazolopiperidine 19 through addition of a Grignard reagent (Scheme 6.11). The *cis* configuration observed in the product was attributed to an  $A^{1,2}$  allylic strain. [24]

Other chiral bicyclic compounds analogous to the preceding ones were recently synthesized by an original method: 2-pyrrolidino-1-ethanol was oxidatively cyclized to the corresponding oxazolopyrrolidines by treatment with  $\text{Me}_3\text{NO}$  [25].

This reaction is catalyzed by an iron carbonyl complex, which led to a 2,4-*trans* geometry of the oxazolidine moiety since, owing to the preferred *cis* ring junction of this [3.3.0] system, this structure is the more stable. Though the mechanism of this process is not fully elucidated, an iminium ion seems to be a likely intermediate (Scheme 6.12).



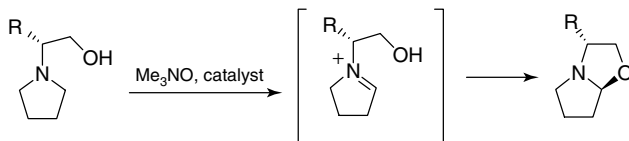
Scheme 6.9



Scheme 6.10



Scheme 6.11

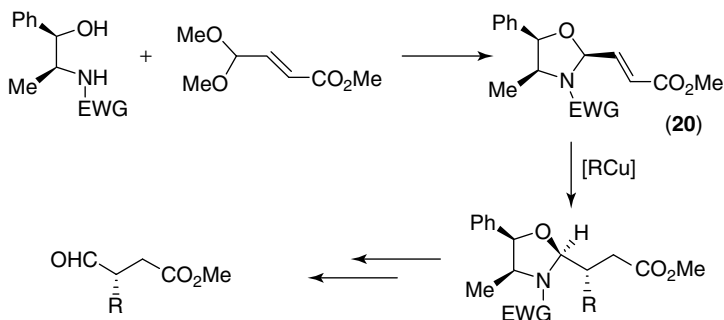


Scheme 6.12

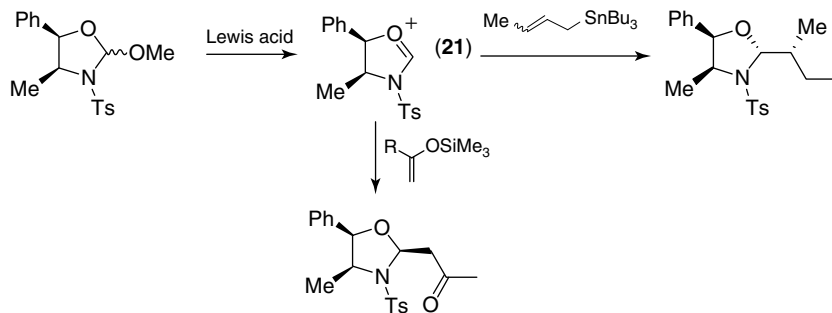
#### 6.1.1.2 *N*-Tosyl and *N*-Boc Oxazolidines

Scolastico *et al.* [26] made use of ketals, instead of aldehydes, as substrates for the synthesis of oxazolidines **20**, which present a very interesting distinctive feature: the heterocycle nitrogen is substituted by various electron-withdrawing groups (EWGs; Cbz, Ts, CO<sub>2</sub>-*t*-Bu, CO<sub>2</sub>Me, etc.). However, the tosyl *N*-substituent proved to be the most productive since it allows the formation of the 2,4-*cis* epimer in a totally stereoselective mode (Scheme 6.13). A structural study [27] showed that, when substituted by this group, the nitrogen is no longer planar (as with the other groups) and, as described above, results in the formation of this thermodynamically favored geometry. A great deal of work has been published that reports the various applications of such oxazolidines as chiral inductors in asymmetric synthesis [1]; most applications concern stereoselective transformations on an unsaturated moiety attached on the C-2 center of the oxazolidine (see an example in Scheme 6.13).

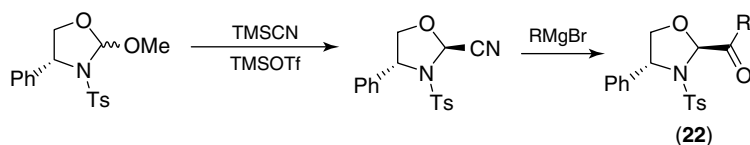
Subsequently, the same authors [28], concurrently with Hoppe's group [29], reported a new stereoselective method of producing stereoisomerically pure *N*-tosyl oxazolidines (Scheme 6.14) via the formation of an intermediate oxocarbenium **21**, reacting with a nucleophile such as an enoxysilane or an allylstanane.



Scheme 6.13



Scheme 6.14



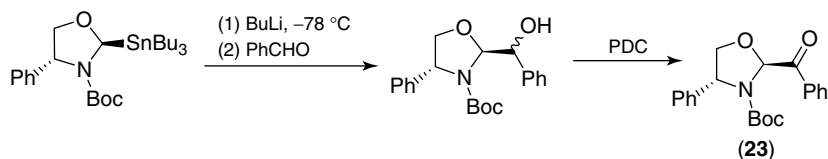
Scheme 6.15

These various methodologies led the way to the synthesis of some of the most useful oxazolidine derivatives: that is, the *N*-tosyl and *N*-Boc-2-acyloxazolidines. Actually, Hoppe [30] published the synthesis (Scheme 6.15) of the *N*-tosyl derivative via the addition the Lewis acid-catalyzed addition of a cyanide ion to an oxocarbenium ion analogous to **21** (Scheme 6.14), and shortly thereafter Colombo [31] described a synthesis of *N*-Boc-2-acyloxazolidine by an organometallic method (Scheme 6.16). Both methods afford very conveniently 2-acyloxazolidines **22** or **23**.

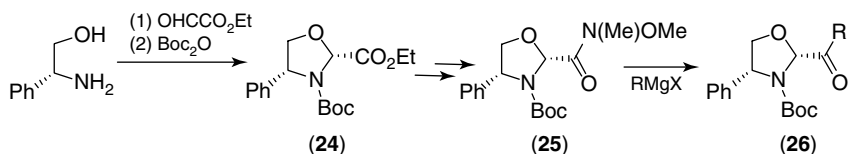
The use of such 2-acyloxazolidines as chiral substrates for many asymmetric transformations was extensively studied by Couty *et al.* [1]. These authors described a new method that affords such synthons (Scheme 6.17) via a condensation between ethylglyoxylate and phenylglycinol or norephedrine [32]. The produced oxazolidines **24**, once saponified, were transformed into their corresponding Weinreb amides **25**, which were, in turn, treated with Grignard reagents in order to produce the required 2-acyloxazolidines **26** in a totally stereoselective way.

Such a methodology allows the formation of a great variety of substrates, which undergo many asymmetric transformations. One example [33] of such a process is given in Scheme 6.18.

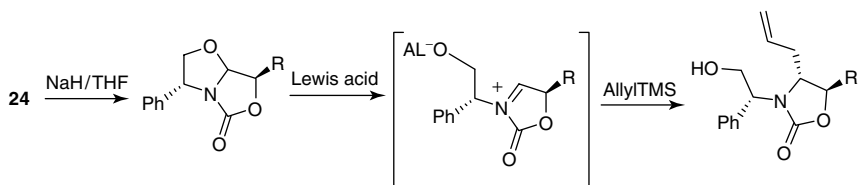
Before closing this paragraph, it is worth mentioning that chiral oxazolidines produced from ketones, instead of aldehydes, have been scarcely described. Besides



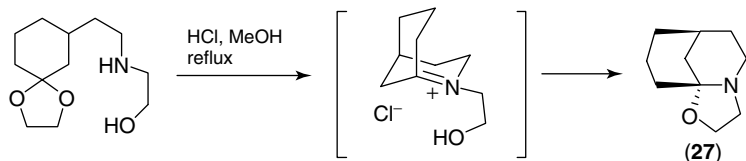
Scheme 6.16



Scheme 6.17



Scheme 6.18



Scheme 6.19

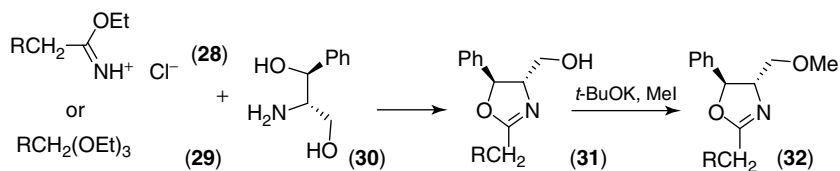
the well-known fact that ketones are much less reactive than aldehydes as regards this type of ketalization, it may be emphasized that in such oxazolidine derivatives the essential control of the geometry of the quaternary C-2 center would be very enigmatic. Clearly, there is no such a problem when this center is not a stereogenic one as in the special case of the oxazolidine derived from acetone, which was recently synthesized by using fluoroalkanesulfonyl azides [34a].

On the other hand, the structural constraints inherent to the tricyclic nature of oxazolidine **27** explain why it was formed as a single diastereoisomer in the reaction depicted in Scheme 6.19 [34b,c]. Interestingly, this cyclization involves the addition on an anti-Bredt iminium ion.

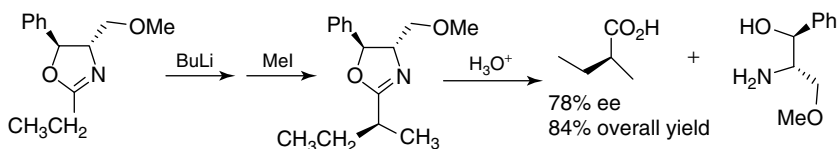
### 6.1.2

#### Oxazolines (4,5-dihydrooxazoles)

In the field of asymmetric synthesis, oxazolines hold a preeminent position, since they come into play as chiral auxiliaries as well as ligands in catalytic systems. Asymmetric carbon–carbon bond formation is of great significance for the synthesis of enantiopure compounds; in this respect, Meyers' methodology, which makes use of such moieties in order to create definite stereogenic centers in carboxylic derivatives, is considered as one of the most fruitful methods in this area [35]. This process was extended with equal success to aromatic substitutions and aryl couplings [36, 37]. On the other hand, oxazoline and, especially, bisoxazolines are recognized as very fruitful ligands for asymmetric catalysis and are concerned with



Scheme 6.20



Scheme 6.21

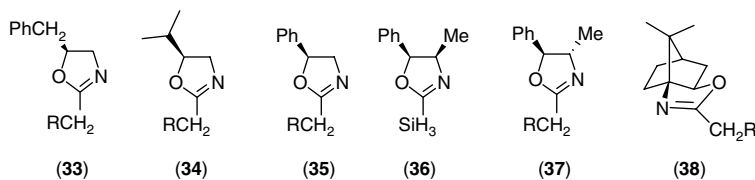
a very impressive array of important reactions, such as for example, aldol reactions, homo- and hetero-Diels–Alder reactions, cyclopropanations, allylic substitutions, and so on [38]. The popularity of these compounds is mainly due to their ease of preparation, which rests on a relatively few but very efficient methods.

As regards the preparation of these versatile heterocycles, it should be underscored that they are masked forms of carboxylic acids; however, carboxylic acids themselves are sometimes inadequate to synthesize oxazolines owing to the weakness of their electrophilic reactivity. Meyers [39] showed that it would be worthwhile to convert them into much more reactive derivatives: that is, imidates of nitriles **28** or orthoesters **29**. These substrates react very smoothly with various enantiopure amino alcohols, and the oxazolines **31** are obtained, maintaining the configuration of the initial stereocenters (Scheme 6.20). The first amino alcohol that was used in this way was (+)-(1*S*,2*S*)-1-phenyl-2-amino-1,3-propanediol **30** (this enantiomer is commercially available since it was a basic material during the industrial synthesis of chloramphenicol). The CH<sub>2</sub>OMe polar appendage in reagent **32** was thought to play a crucial role during the asymmetric transformations that were operated on the carboxylic moiety. Indeed, it can act as a ligand, which, jointly with a nitrogen atom, chelates a metal cation (in the most cases Li<sup>+</sup>), thereby forcing the attacking nucleophile to enter from a specific side of the molecule.

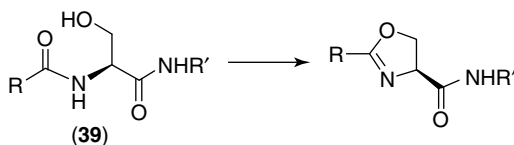
Once the subsequent asymmetric transformation is realized, the amino alcohol is easily recovered from the acidic hydrolysis of the product (see Scheme 6.21 for an example).

Since then, many other amino alcohols have been employed in order to synthesize such chiral oxazolines [40]. Among them, the usual reduced derivatives of  $\alpha$ -amino acids and derivatives of the ephedrine family frequently reported as substrates (Scheme 6.22) are phenylalaninol **33**, valinol **34**, phenylglycinol **35**, ephedrine **36**, pseudoephedrine **37**, and so on. Special mention may be made to a camphor-derived amino alcohol **38**, which leads to oxazolines whose carboxylic moiety was alkylated with excellent diastereoselectivity without the need for any polar appendage [41].

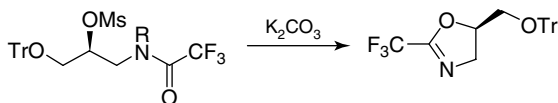




Scheme 6.22



Scheme 6.23



Scheme 6.24

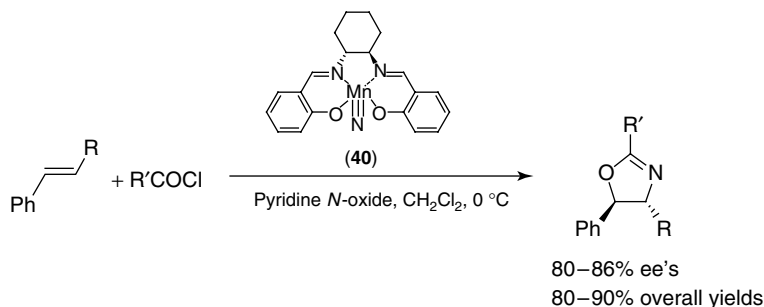
Actually, Meyers has observed that such extra ligands may not always be necessary in order to achieve highly stereoselective synthesis [37].

Apart from their outstanding involvement in asymmetric synthesis, enantiopure oxazolines are found as elements of miscellaneous natural products and biologically active molecules [42]. Therefore, it is understandable that a great deal of work has been devoted to their preparation.

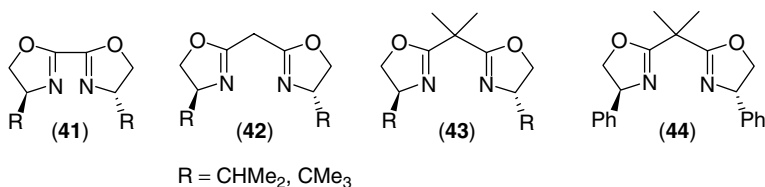
The most expeditious way of synthesizing 1,2-oxazolines is the reaction of 1,2-amino alcohols (belonging to or simply derived from the chiral pool) with acid derivatives as presented by Meyers (see above). Intramolecular substitution has also contributed to such syntheses. Thus, various dehydrating catalysts have been reported as being effective in the dehydrative cyclizations of *N*-acyl- $\beta$ -hydroxy- $\alpha$ -amino acid amides **39** (Scheme 6.23), and a catalytic procedure using molybdenum oxide has recently been reported for the corresponding reaction applied to *N*-acylserine and *N*-acylthreonine derivatives [43].

Another type of a related intramolecular cyclization involves the amide group as the nucleophile (Scheme 6.24). In this case, the hydroxy moiety has to be converted into mesylate and the ring closure occurs stereospecifically with inversion [44]. This procedure has the advantage of allowing the formation of oxazolines substituted only on the C-5 center; these compounds are otherwise difficult to obtain owing to the lack of accessibility of the corresponding amino alcohols.

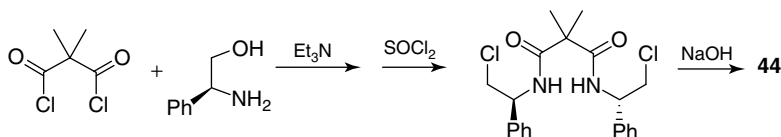
To the best of our knowledge, there is only one work reporting a genuine enantioselective synthesis of enantiopure oxazolines (all the other cases actually are mostly diastereoselective processes). Komatsu *et al.* [45] described the transformation of styrene (Scheme 6.25) derivatives into optically active oxazolines when they are reacted with acyl chlorides in the presence of the salen complex **40**.



Scheme 6.25



Scheme 6.26

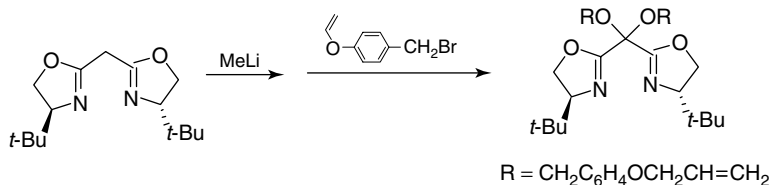


Scheme 6.27

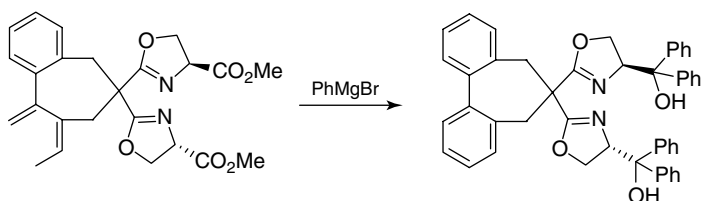
The first report of chiral oxazolines as ligands for catalytic asymmetric transformations goes back to 1986 [46]. Since then, much work has been devoted to the preparation and application of these compounds, and, as mentioned before, a number of reviews have covered this topic [38]. However, the seminal studies by both Evans [47a] and Corey [47b] (Scheme 6.26) should not be overlooked because they introduced the exceptionally fruitful C<sub>2</sub>-symmetric bisoxazoline ligands 41–43 [47a] and 44 [47b] in this field (Box ligands).

The procedure that was used to prepare these first Box ligands is univocal: the spacer comes from a symmetrically disubstituted malonic acid derivative, and the cyclization from the chiral aminoalcohol moiety is somewhat trivial (Scheme 6.27). This procedure still is the most used one, and many variants have been presented, in particular by Denmark [48] and Hanessian [49]: sulfonates as leaving group, various dehydrating agents, malononitrile instead of malonyl chloride, and so on. All these interesting variants have been extensively described in Desimoni and Jorgensen's review [38d].

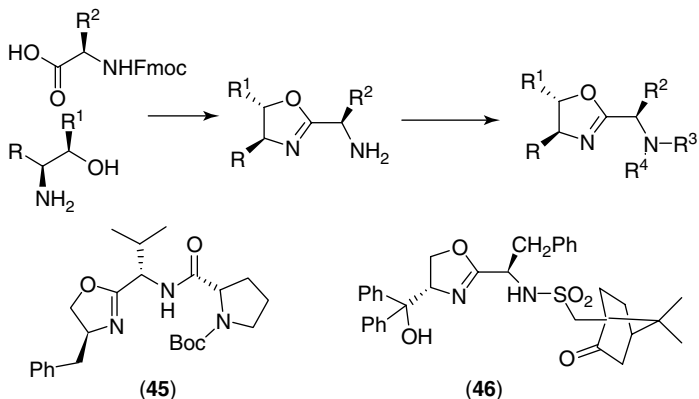
The second general procedure can be viewed as an extension of the preceding one; it is based on the substitution of the methylene hydrogens of the malonyl moiety and has led to numerous other Box ligands (see Scheme 6.28 for a representative example [50] of this method).



Scheme 6.28



Scheme 6.29



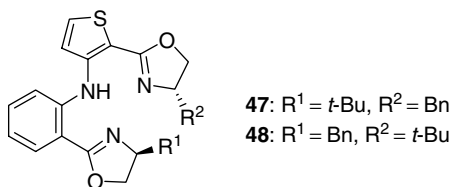
Scheme 6.30

Another procedure consists in the manipulation of groups already present in the ligand or in the spacer as depicted in Scheme 6.29 [51].

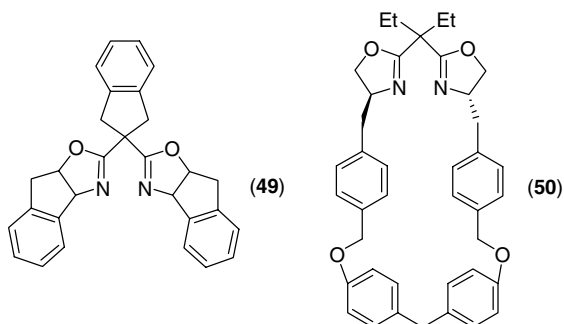
Recently, nonsymmetric Box-containing ligands appeared to be very promising in the asymmetric catalysis of various reactions. Thus, Sigman exploited a modular approach to ligands (for example **45** and **46**) composed of both oxazoline and another basic moiety (Scheme 6.30) acting as templates during the catalysis of enantioselective Diels–Alder reaction [52a], addition of allylic halides to aldehydes [52b] as well as addition of allyl bromide to ketones [52c].

Very recently, another set of 16 nonsymmetrical Box ligands were tested in the chromium-catalyzed Nozaki–Hiyama–Kishi allylation of benzaldehyde [53]. Compounds **47** and **48** are the most promising in this respect (Scheme 6.31).

Now, we cannot overemphasize the remarkable creativity that is still displayed in this field, and a large number of various ligands have been prepared and tested in



Scheme 6.31



Scheme 6.32

a variety of metal-catalyzed enantioselective reactions (see for instance compounds 49 [54] and 50 [55] in Scheme 6.32).

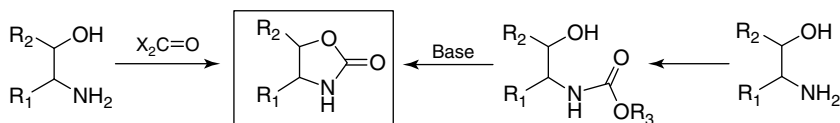
Extensive research is still ongoing in this very fruitful field, and recently the use of such ligands supported on poly(ethylene glycol) has been reported [56]; enantioselective catalysis can thus be envisioned in aqueous solution.

### 6.1.3

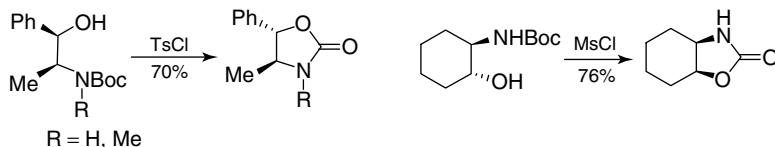
#### Oxazolidinones

##### 6.1.3.1 Oxazolidin-2-ones

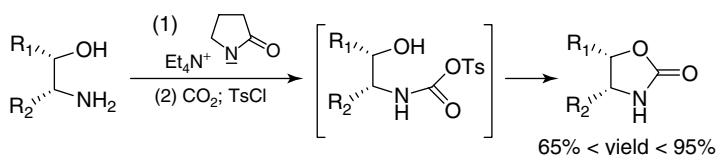
Oxazolidin-2-ones constitute an important class of oxazolidine derivatives. Since the first report in 1981 [57], chiral oxazolidin-2-ones (namely, Evans auxiliaries) have been widely used as chiral auxiliaries in numerous asymmetric organic reactions [58, 59], such as aldol condensations [60], Diels–Alder reactions [61], 1,3-dipolar cycloadditions [62], and radical reactions [63]. Moreover, since the 1980s, oxazolidinones represent an exciting new class of synthetic antibacterial agents [64]. Given the high synthetic utility of these heterocycles, asymmetric synthesis of oxazolidinones has attracted much attention. As the oxazolidines described above, one of the important chiral sources for the preparation of enantiopure 1,3-oxazolidin-2-ones is  $\beta$ -amino alcohols [65]. Reactions of amino alcohols with carbonyl derivatives such as phosgene [66], trichloromethylchloroformate (diphosgene) [67, 68], triphosgene [69], carbonyldiimidazole [70], and diethylcarbonate [71] have led to oxazolidinones in which the configurations of the stereocenters of the starting amino alcohols are retained. The construction of oxazolidinones from *N*-carbamate derivatives of



Scheme 6.33



Scheme 6.34



Scheme 6.35

1,2-aminoalcohols occurred also without changes in the configuration of the carbon bearing the hydroxyl group, when the carbamate was treated by a base, as shown in Scheme 6.33 [72, 73].

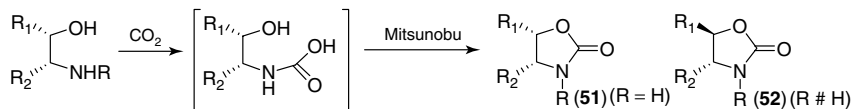
In contrast, an inversion of configuration, as depicted in Scheme 6.34, was observed via an  $S_N2$  pathway from *N*-Boc derivatives of 1,2-amino alcohols, when the hydroxyl group was transformed into a good leaving group (reaction with TsCl [74], MsCl [75]).

With the aim of finding methodologies involving the use of harmless materials in place of toxic reagents such as phosgene, Feroci *et al.* used carbon dioxide in the presence of 2-pyrrolidone electrogenerated base and tosyl chloride (Scheme 6.35) [76]. In this methodology, the absolute configuration of all chiral atoms is retained; this result excludes the tosylation of the hydroxyl group.

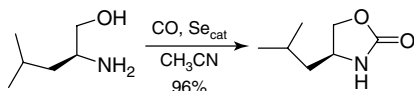
Carboxylation followed by a Mitsunobu reaction has been investigated [77]. These reactions occurred with high yields. The stereochemical course of the Mitsunobu reaction is dependent on the *N*-substituent: primary amines gave oxazolidinones **51** with retention of configuration at the oxygen-bearing center, while secondary amines led to oxazolidinones **52** with inversion of configuration at the oxygen-bearing center (Scheme 6.36). Experiments with  $^{18}\text{O}$ -labeled carbon dioxide evidenced two distinct mechanisms during the cyclization step [77b].

Chiral oxazolidinones were synthesized by using the selenium-catalyzed carbonylation of the corresponding 2-amino alcohols by bubbling CO at atmospheric pressure without racemization (Scheme 6.37) [78].

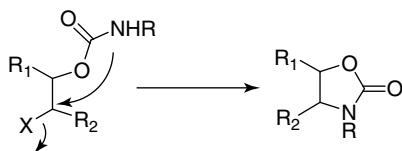
An alternative strategy involves the intramolecular displacement of a leaving group by the nitrogen atom of a *N*-benzoyl or *N*-tosyl carbamate (Scheme 6.38). The leaving group can be a bromine [79], a phenylselenide substituent [80]. The



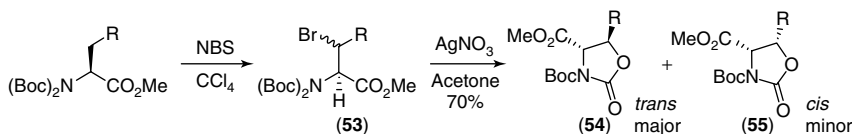
Scheme 6.36



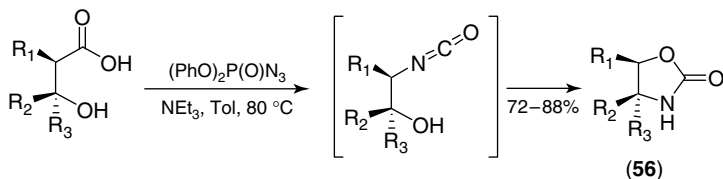
Scheme 6.37



Scheme 6.38



Scheme 6.39

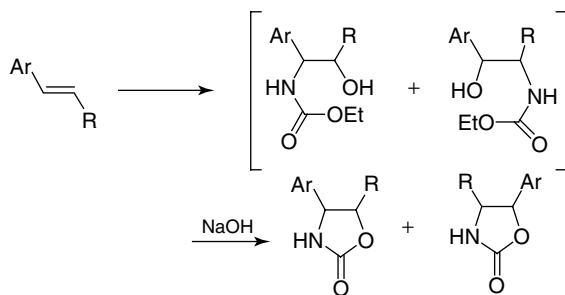


Scheme 6.40

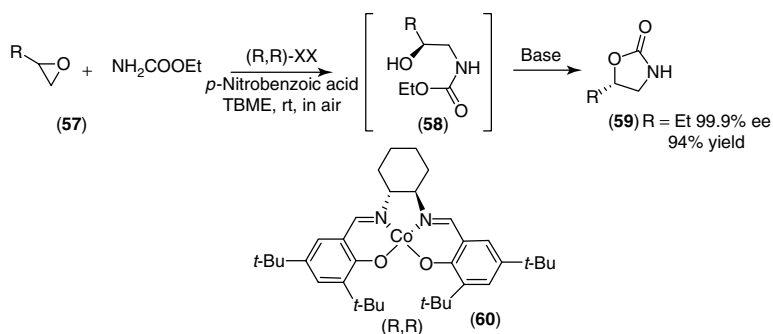
oxazolidinone ring was also generated by a similar intramolecular nucleophilic addition, in basic media, to a vinyl sulfoxide moiety [81] or an epoxide [82].

Crich and Banerjee reported an expedient synthesis of oxazolidinones from  $\alpha$ -amino acids, as precursors of  $\beta$ -hydroxy- $\alpha$ -amino acids (Scheme 6.39). [83] The *N*-bromosuccinimide (NBS)-mediated radical bromination of *N*, *N*-di-*tert*-butoxycarbonyl-protected  $\alpha$ -amino acids afforded a 1:1 mixture of the diastereoisomeric bromide **53**, which was treated with silver nitrate to give predominantly the *trans*-oxazolidinones **54**.

Formation of acyl azide from chiral  $\beta$ -hydroxy- $\alpha$ -amino acids, Curtius rearrangement and internal cyclization afforded 4-substituted and 4,5-disubstituted oxazolidin-2-ones **56** in good yields and with complete stereochemical control, as described in Scheme 6.40 [84].



Scheme 6.41

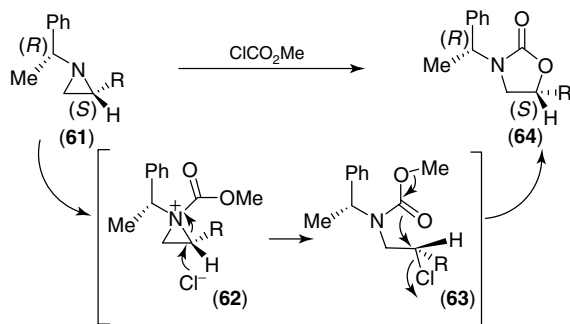


Scheme 6.42

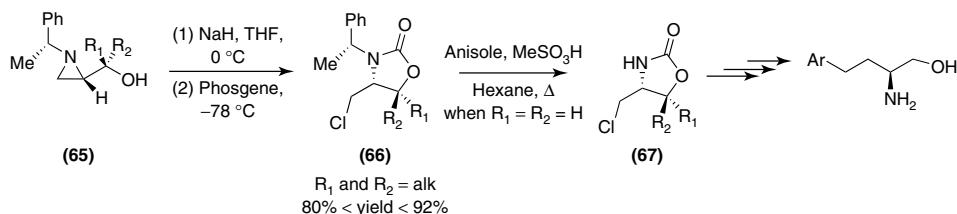
In the following approach, the authors envisioned the use of the Sharpless asymmetric amino hydroxylation of a styrene derivative followed by a base-mediated selective ring closure of the resulting carbamate to afford oxazolidinones in a single step (Scheme 6.41). The optimized aminohydroxylation conditions were used on several  $\beta$ -substituted styrene derivatives [85].

Bartoli *et al.* reported a methodology that provided a simple and practical tool for synthesizing a collection of varied 5-substituted oxazolidinones in almost enantiomerically pure form from racemic terminal epoxides [86]. The asymmetric carbamate-based aminolytic kinetic resolution (AKR) of racemic epoxides **57** catalyzed by Jacobsen's (salen)-Co<sup>III</sup> chiral complex **60**, which was generated *in situ* by oxidation of the catalytically inactive (salen)-Co<sup>II</sup> complex, gave *N*-protected 1-amino-2-ol **58** in almost enantiomerically pure form (Scheme 6.42). The best base to promote the subsequent cyclization step was sodium hydride. This one-pot reaction sequence appeared as an easy and very convenient protocol to access a wide range of enantiopure 5-substituted oxazolidinones **59**.

5-Functionalized enantiomerically pure oxazolidin-2-ones **64** were also prepared in one pot from commercially available chiral aziridines **61** bearing an EWG at C-2 (R = ester, vinyl or acyl, Scheme 6.43) [87]. The reaction was performed with methyl chloroformate to give a high yield (up to 85%) of the 5-functionalized oxazolidinones. This reaction occurred with retention of the configuration through an S<sub>N</sub>2-type double inversion process: acylation on the nitrogen to form the



Scheme 6.43



Scheme 6.44

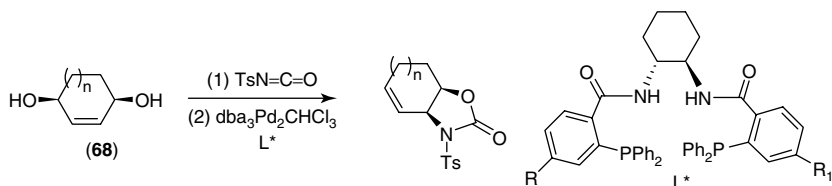
activated aziridinium species **62**, which was regioselectively cleaved by chloride ion via an  $\text{S}_{\text{N}}2$  process, followed by intramolecular cyclization by the carbamate moiety.

The same authors reported a novel and efficient pathway to oxazolidinones from aziridines **65** [88]. Treatment of these compounds with sodium hydride and phosgene led to enantiopure (chloromethyl)-5-substituted-oxazolidin-2-ones **66**. Phosgene was selected as the intramolecular cyclizing agent of the amino alcohol moiety in order to form the cyclic carbamate with regioselective ring opening of the aziridine by the chloride ion (Scheme 6.44). The oxazolidinone **67** ( $\text{R}_1 = \text{R}_2 = \text{H}$ ) was then transformed into enantiopure (L)-homophenylalaninol derivatives.

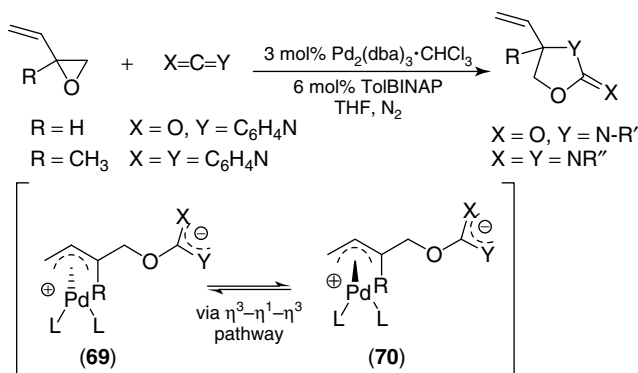
Trost and coworkers have investigated the palladium-catalyzed desymmetrization of meso biscarbamates. [89] The oxazolidinone-forming reaction was easily carried out by preparing the biscarbamate substrate *in situ* from the *cis*-diol **68**, and the biscarbamate solution was added to a solution of 5 mol% catalyst, prepared by stirring a mixture of ligand (L) and tris(dibenzylideneacetone)dipalladium–chloroform complex. The best yields and enantiomeric excesses (84% yield and  $>99\%$  ee for  $n = 1$ ) were obtained by using  $\text{L}^*$  with  $\text{R} = \text{R}_1 = \text{H}$  and by adding triethylamine to the mixture (Scheme 6.45). The origin of the enantioselectivity was explained by a model suggesting that the difference in diastereotopic transition states (ionization of the pro-*S* leaving group vs. ionization of the pro-*R* leaving group) was the result of steric interactions between the chiral ligand and the cycloalkene.

Larksarp and Alper reported a highly enantioselective method for the synthesis of oxazolidinones by palladium(0) catalyzed cycloaddition of vinyloxiranes with heterocumulenes such as carbodiimides or isocyanates by using chiral phosphine ligands [90]. Oxidative addition of the chiral phosphine–palladium complex

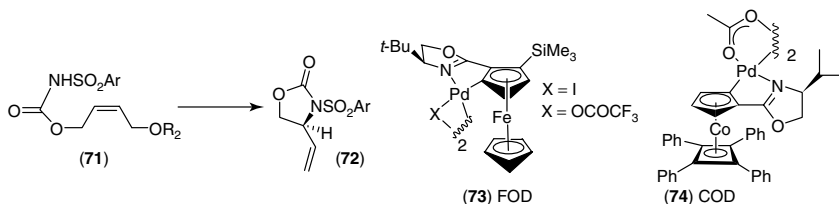




Scheme 6.45



Scheme 6.46

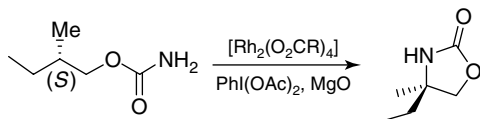


Scheme 6.47

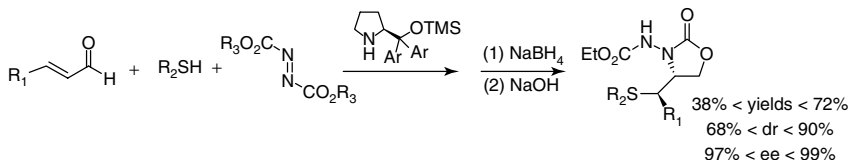
to racemic vinyl oxirane followed by heterocumulene complexation led to a diastereoisomeric  $\pi$ -allyl palladium complexes **69** and **70**, which are equilibrated via an  $\eta^3-\eta^1-\eta^3$  mechanism (Scheme 6.46). This equilibrium is much faster than the nucleophilic addition of the nitrogen.

Cyclization of the allylic *N*-arylsulfonylcarbamates **71** (prepared from allylic alcohol and arylsulfonylisocyanate) catalyzed by ferrocenyloxazoline palladacycles (FOP) afforded 4-vinyl-2-oxazolidin-2-ones in high yields and enantioselectivities. A better catalyst was recently found by the same authors: the cobalt oxazoline palladacyclic complex **74** that does not require preactivation like the FOD complexes (Scheme 6.47) [91].

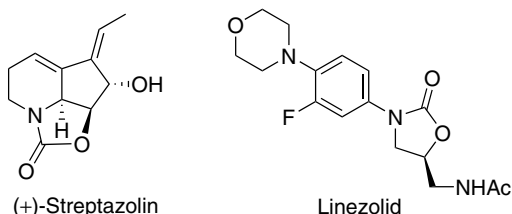
Lespino and Du Bois described the catalytic oxidative cyclization of various carbamates to oxazolidinones [92]. The reactions were performed optimally using  $[\text{Rh}_2(\text{OAc})_4]$  as catalyst,  $\text{PhI}(\text{OAc})_2$  as oxidant and  $\text{MgO}$  as base additive



Scheme 6.48



Scheme 6.49



Scheme 6.50

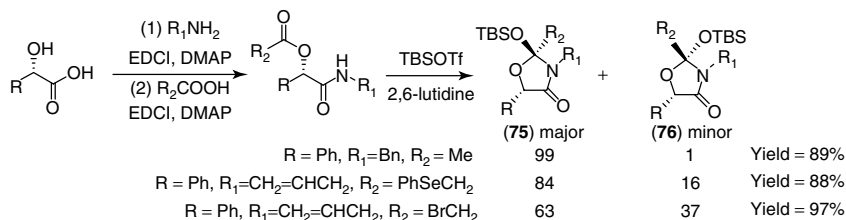
(Scheme 6.48). The authors showed that the C–N bond formation is totally stereoselective and postulated a metal-directed N-atom insertion process. This method is significant because it gives access to quaternary  $\alpha$ -amino acids.

A very efficient asymmetric multicomponent reaction [93] involving both enamine and iminium activation gave access to highly functionalized oxazolidinones (Scheme 6.49). The domino-conjugated nucleophilic addition of thiols to  $\alpha,\beta$ -unsaturated aldehydes in the presence of 2-[bis(3,5-bis(trifluoromethyl)phenyl)pyrrolidine-1-yl]trimethylsilyloxymethylpyrrolidine as catalyst, followed by electrophilic amination reaction to the enamine intermediate, resulted in the formation of nearly enantiopure oxazolidinones.

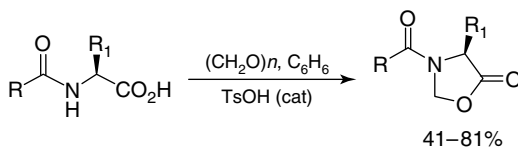
Many recent works have reported the asymmetric synthesis of oxazolidinones via asymmetric desymmetrization of prochiral diols. Serinol derivatives were used to give enantiomerically enriched monoacetates, which were transformed by appropriate reactions into oxazolidinones [94].

Besides the importance of oxazolidinones as chiral auxiliaries, these compounds also constitute a new class of antimicrobial compounds, which were discovered by researchers at Dupont in the 1980s [95]. The oxazolidinone moiety was found in the structure of few biologically active natural products such as (–)-cytoxazone [96] or (+)-streptazolin [97], and much effort has been devoted to the development of analogs (Scheme 6.50).

Actually, these compounds exert potent *in vitro* and *in vivo* antibacterial activity against multiple antibiotic-resistant strains of Gram-positive bacteria. Linezolid [98] was the first oxazolidinone that was introduced into clinical trials and approved



Scheme 6.51



Scheme 6.52

in 2000 by the Food and Drug Administration. Many enantioselective syntheses of these products and their analogs have been described by using the classical reactions, cited above, to generate the oxazolidinone ring.

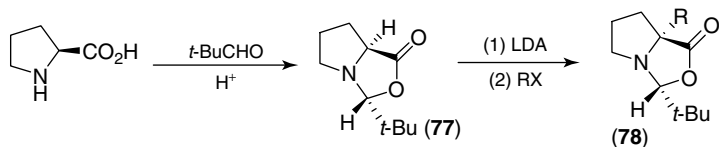
#### 6.1.3.2 Oxazolidin-4-ones and 5-ones

Only a few reports are devoted to the asymmetric synthesis of 4-oxazolidinones. Kamimura *et al.* [99] described in 2002 the synthesis of a new type of heterocycles: the oxyoxazolidinones **75** and **76** (Scheme 6.51), which are readily prepared from O-acylmandelamides on treatment with TBSOTf.

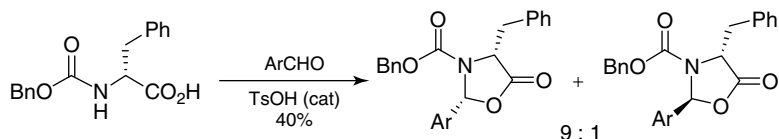
These compounds were used by the same authors as chiral auxiliaries for heterocyclic synthesis [100].

Although much less used than the oxazolidin-2-ones, 5-oxazolidinones are attractive precursors for the synthesis of various substituted amino acids [101]. Ben-Ishai [102] was the first to describe the reaction between *N*-Cbz-amino acids with paraformaldehyde, under acid catalysis, that led to 5-oxazolidinones via an intramolecular cyclization. With a view to synthesizing *N*-methyl amino acids, several chemists extended the range of substrates that can be transformed into 5-oxazolidinones, and different protecting groups (*N*-Fmoc [103], *N*-Cbz, *N*-Boc [104] were used to develop this methodology (Scheme 6.52). Recently, Hughes *et al.* [105] described the syntheses of *N*-methyl amino acids of the common 20 amino acids in high yields and without racemization via 5-oxazolidinone intermediates.

The synthesis of  $\alpha,\alpha'$ -disubstituted amino acids from a bicyclic oxazolidinone was first developed by Seebach and coworkers [106]. Reaction between proline and pivalaldehyde under acidic catalysis gave the single product **77**, in which the *tert*-butyl group is on the *exo* face, in a *cis* relationship with the bridgehead hydrogen. No epimerization occurred during this condensation. Deprotonation and alkylation led to the products **78** in moderate to excellent yields and with essentially complete diastereoselection (Scheme 6.53). Recently, Vartak *et al.* [107] described a stereoselective synthesis of  $\alpha,\alpha'$ -biprolines by using this procedure.



Scheme 6.53



Scheme 6.54

This methodology has been applied to acyclic amino acids with moderate yields. The procedure involves an aromatic aldehyde [108, 109] or pivalaldehyde [110] and afforded a separable mixture of oxazolidinones, whose major isomer showed a *cis* configuration, as depicted in Scheme 6.54.

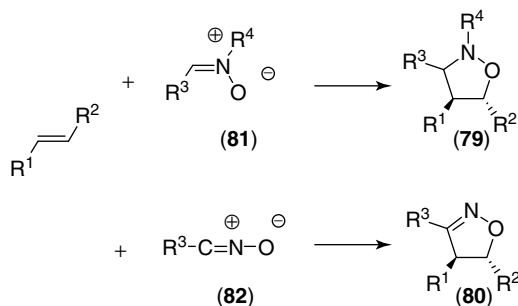
Most of the syntheses described here are based on stereoselective synthesis using chiral precursors (amino alcohols, amino acids, hydroxy acids, aziridines, etc.). But, during the last few years, new strategies using asymmetric catalysis to obtain enantioenriched oxazolidinones have emerged. They have contributed to widening the field of application of these compounds as chiral auxiliaries and as biologically active compounds.

#### 6.1.4

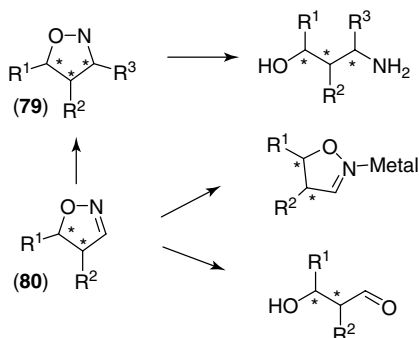
##### Isoxazolines and Isoxazolidines

As clearly suggested by the presence of their N–O bond, isoxazolidines **79** and isoxazolines **80** are commonly prepared (Scheme 6.55) through 1,3-dipolar cycloaddition reactions [62, 111] from alkenes and nitrones **81** or nitrile oxides **82**, respectively.

As it will be detailed below, isoxazolidines **79** are especially valuable reagents for synthetic purposes, whereas isoxazolines **80** essentially constitute the basis



Scheme 6.55



Scheme 6.56

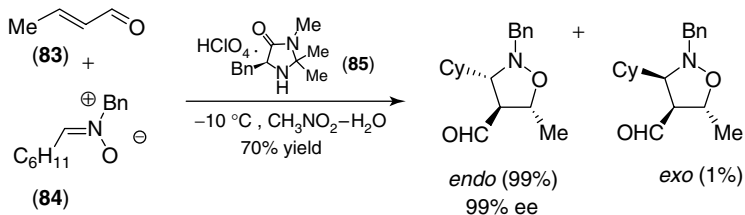
for meaningful ligands that are used during various metal-catalyzed reactions (Scheme 6.56).

#### 6.1.4.1 Isoxazolidines

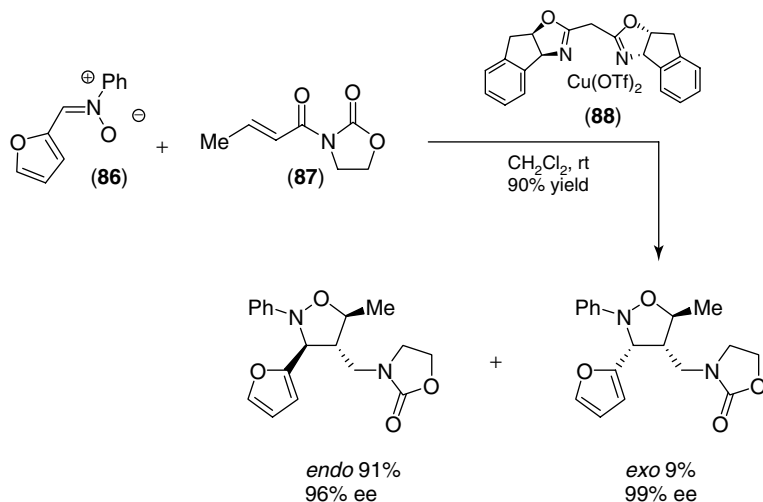
Chiral isoxazolidines are known for a long time as valuable intermediates in the synthesis of many important classes of molecules: alkaloids,  $\beta$ -amino acids,  $\beta$ -lactams, amino sugars, and so on. This is due to the labile nature of their N–O bond; isoxazolidines can be viewed as masked forms of  $\gamma$ -amino alcohols and they are easily prepared in an enantiopure form from chiral nitrones or chiral alkenes or also, to a lesser extent, from both chiral nitrones and alkenes [112]. Intermolecular as well as intramolecular [3 + 2] cycloadditions have been performed and the recent use of metal catalysis was especially examined [62, 111, 113].

First, it should be underscored that such reaction creates up to three stereogenic centers and, irrespective of the enantioselectivity issue, this fact requires that regio- and diastereoselectivities are controlled [114]. The classical endo/exo problem adding further to these difficulties, much work has been devoted to circumvent these points [111, 115].

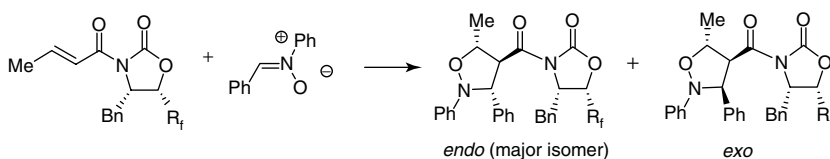
For instance, MacMillan [116] (Scheme 6.57) described an example of remarkable control of all these selectivities by using crotonaldehyde **83** (the presence of the EWG on the alkene clearly directs the regioselectivity on the dipolarophile) reacting with nitrone **84** in the presence of the imidazolidinone salt **85**, which acts as the chiral organocatalyst.



Scheme 6.57



Scheme 6.58



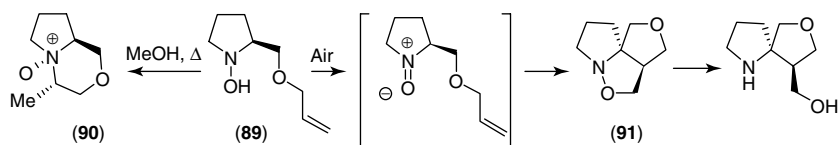
Scheme 6.59

The improvement of the diastereofacial selectivity provoked by the presence of a Lewis acid is common in the cycloaddition field. This can be also substantiated in the present case as shown in Scheme 6.58, which depicts the enantioselective reaction of nitron **86** with dipolarophile **87** under the catalytic effect of a chiral bisoxazoline/Lewis acid complex **88** [117a].

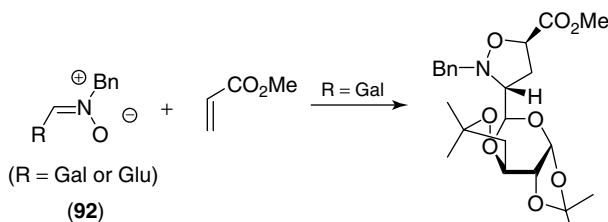
Nitron cycloaddition of a fluorinated oxazolidinone chiral auxiliary catalyzed by Yb(OTf)<sub>3</sub> or Sc(OTf)<sub>3</sub> was reported [118] to give cycloadducts with excellent yields and stereoselectivities (Scheme 6.59). This initial work stimulated intensive research in the field of fluorinated-supported auxiliaries [119] in order to make use of such reactions for specific synthesis purposes [73, 120] or for elaborating combinatorial libraries [121].

Interestingly, *N*-oxide derivative **90** was produced via a reverse-Cope elimination from hydroxylamine **89** [122]; on the other hand, after being oxidized by air, hydroxylamine **89** reacted intramolecularly to afford the spiro tricyclic isoxazolidine **91** with excellent diastereoselectivity. Eventually, the N–O bond was cleaved with zinc, yielding a hydroxylamine, as shown in Scheme 6.60. Similar strategies were described by others later on [123].

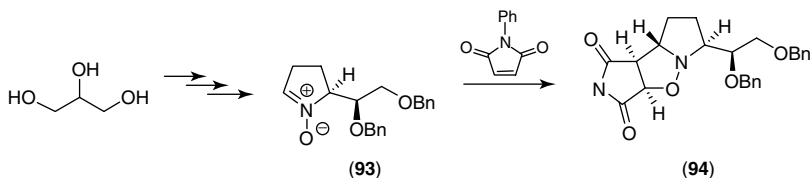
As might be anticipated, nitrones derived from natural products have given rise to numerous studies. Two of these (Scheme 6.61) may serve as examples of this fruitful area. First, highly regio- and stereoselective cycloaddition of methyl acrylate



Scheme 6.60



Scheme 6.61



Scheme 6.62

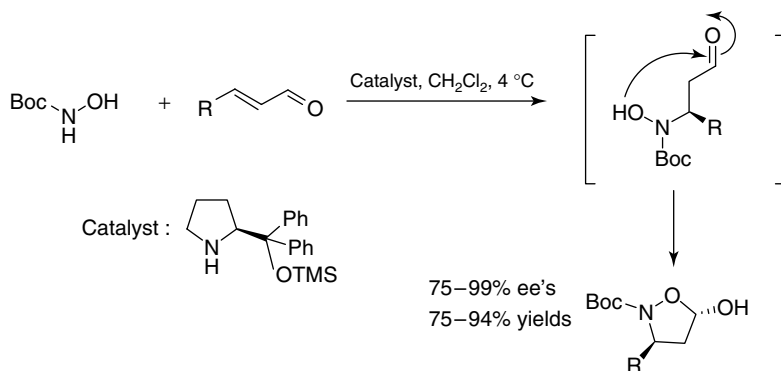
to nitrones **92** derived from D-galactose and D-glucose afforded starting material for the synthesis of complex molecules [124].

The second example [125] is related to nitron **93**, synthesized from a D-glyceraldehyde derivative, which shows complete regio- and stereoselectivities when it reacts with a large range of dipolarophiles. For instance (Scheme 6.62), its reaction with N-phenyl succinimide produced compound **94** in an exclusive *exo/anti* cyclization mode.

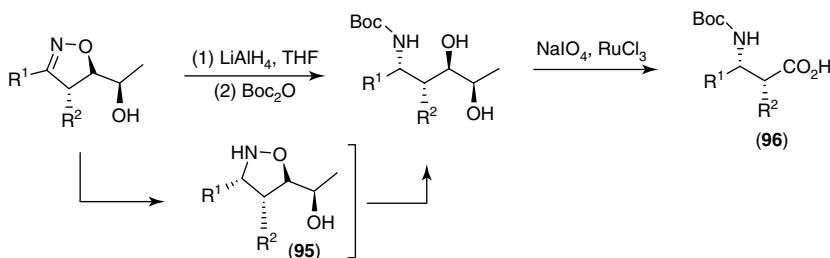
An attractive organocatalytic synthesis of 5-hydroxyisoxazolidines has been described by Cordova *et al.* [126]. These authors made use of a tandem reaction involving hydroxylamines and  $\alpha$ ,  $\beta$ -ethylenic aldehydes as reagents (Scheme 6.63); the target compounds offer a versatile entry to the synthesis of different  $\beta$ -amino acids and  $\gamma$ -amino alcohol derivatives.

#### 6.1.4.2 Isoxazolines

2-Isoxazolines are also prepared from a [3 + 2] cycloaddition reaction to alkenes, the reagents here being nitrile oxides (Scheme 6.55) [127]. They can be prepared as single stereoisomers when the chiral allylic alcohol is a dipolarophile [128]. Synthesis of such heterocycles as well as their applications have been intensively reviewed [62, 111] and this can be easily understood given the usefulness of such compounds, in particular, as starting material for the synthesis of amino acids [129] and as chiral ligands in metal-catalyzed reactions [130].



Scheme 6.63



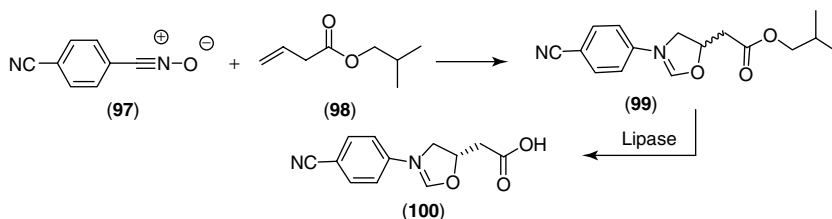
Scheme 6.64

It could be first mentioned that isoxazoline can be transformed into their saturated homologs, namely, the isoxazolidines (see above), with advantageous control of the created stereogenic center at the C-3 position. For instance, Mapp *et al.* [129] reported stereoselective hydride addition to the C-3 C=N bond of the unsaturated heterocycle in order to obtain intermediate isoxazolidines **95**, which were then transformed into  $\beta$ -amino acids **96** (Scheme 6.64). Similar reactions were also described by using Grignard and organolithium reagents.

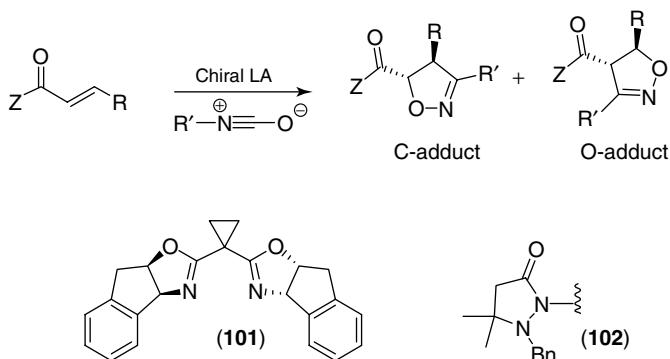
Though enantiopure isoxazolidines are commonly produced when starting from either chiral reagents or chiral catalyst, racemic isoxazolidine can be resolved by using lipases. In this way, condensation of achiral nitrile oxide **97** and isobutyl vinylacetate **98** afforded racemic isoxazoline **99**. However, enzymatic hydrolysis with lipase PS30 operates smoothly a kinetic resolution, yielding the enantiopure isoxazoline acid **100** (Scheme 6.65) [131].

The effect of Lewis acids linked to a bisoxazoline ligand gave rise to a recent, interesting study about the control of regioselectivity which can be crucial during the nitrile oxide cycloaddition. Sibi *et al.* [132] recently made a careful examination of the different factors that affect this selectivity and delineated the role of various Z templates and Lewis acids in the relative production of the C-adduct and the O-adduct (Scheme 6.66). The higher regioselectivity as well as the best enantioselectivity was obtained by using  $\text{MgI}_2$  linked to the ligand **101** and the achiral pyrazolidinone template **102**.

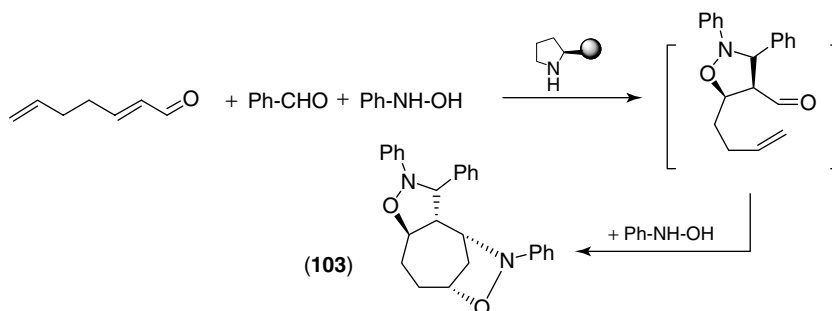




Scheme 6.65



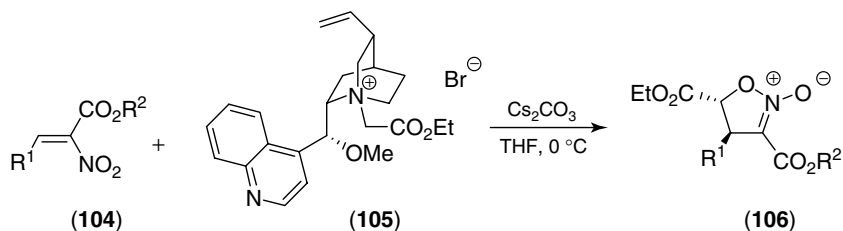
Scheme 6.66



Scheme 6.67

Actually, very enantioselective processes have been described as the outcome of the 1,3-dipolar cycloaddition reactions that lead to isoxazolidines when mediated by a chiral Lewis acid, and it is meaningful to note that Box ligands (see above) appear as the most appealing ones [133]. Apart from these processes involving chiral catalysts, the most common ones are definitely the use of chiral nitrile oxides or chiral alkenes; both processes have been extensively reviewed [111].

Recently, it has been reported [134] that a supported proline catalyst can be used for a three-component intermolecular [3 + 2] cycloaddition, which is displayed in Scheme 6.67. Tricyclic bis-isoxazoline **103** was thus obtained with an outstanding



Scheme 6.68

stereocontrol (>25:1 dr and 99% ee) during the formation six new bonds and five new stereocenters.

In conclusion, it is interesting to note that a recent preliminary report describes a very stereoselective synthesis of isoxazoline *N*-oxides [135]. In the presence of cesium carbonate, nitroolefins **104** reacted with the ammonium salt **105** of cinchonidine to afford nitrile oxides **106** with utmost dia- and enantioselectivities (Scheme 6.68).

## 6.2

### Five-Membered Heterocycles with Two N Atoms

#### 6.2.1

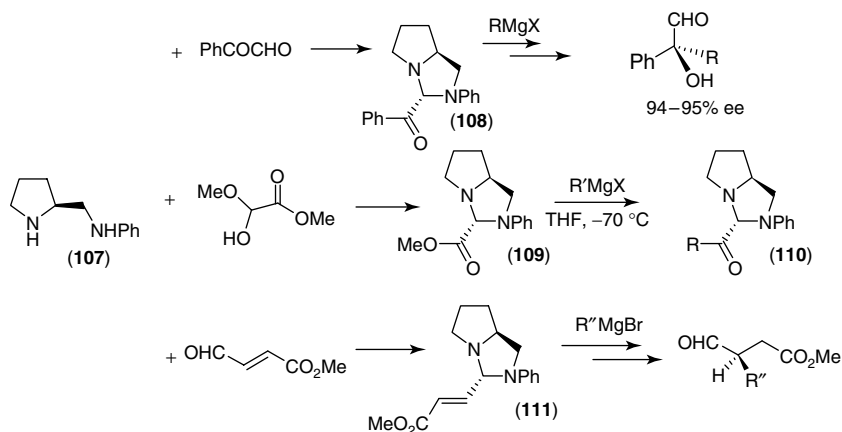
##### Imidazolidines and Imidazolidinones

##### 6.2.1.1 Imidazolidines

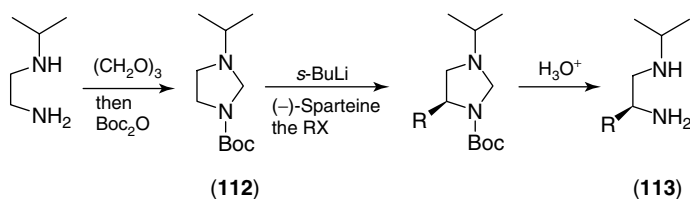
At the end of the 1970s, Mukaiyama [136] reported the first efficient asymmetric synthesis, which was based on the use of chiral diamino ligands (including heterocyclic ones), and since then this field is continuously growing [137]. As will be developed below, preparations of imidazolidine derivatives and oxazolidine (see above) are similar; however, it should be noted at the onset that the chiral pool does not furnish diamines as abundantly as the amino alcohols, which are the starting material for the synthesis of oxazolidines.

Actually, the condensation of chiral diamines with aldehydes produces imidazolidines smoothly, which are rather fragile compounds (as every aminal is), and care is needed during the hydrolysis process. Scheme 6.69 shows Mukaiyama's preparation of compounds **108–111** from diamine **107** derived from (*S*)-*N*-benzyloxycarbonylproline. These *N*-acylimidazolidines were reported to be very efficient chiral auxiliaries for remarkably enantioselective Grignard 1,2 or 1,4 additions. The 2*R* configuration of the aminals was produced exclusively, and this has been explained by its less crowded structure compared to that of its 2*S* epimer [138].

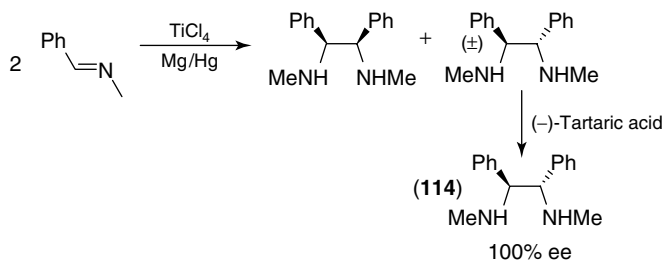
As mentioned above, enantiopure 1,2-diamines are not very commonly obtained from the chiral pool, and an original way for supplying for these heterocycles was reported (Scheme 6.70) [139]. It consists of asymmetric deprotonation of an achiral imidazolidine **112** carried out by butyl lithium in the presence of sparteine, and the resulting anion was then reacted with an alkyl halide, the eventual ring opening



Scheme 6.69



Scheme 6.70

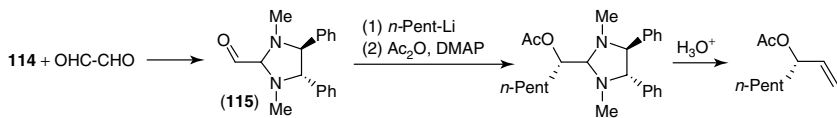


Scheme 6.71

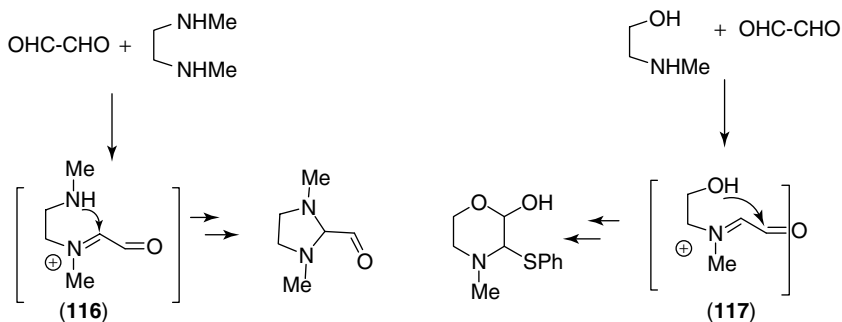
and deprotection of the amino group allowing the synthesis of many optically active 2-alkyl diamines 113.

The fact that such diamines are not easily attainable is also illustrated by the formation of *N*, *N'*-dimethyl-1,2-diphenylethylenediamine in the racemic form via a reductive coupling reaction with low-valent titanium species (Scheme 6.71). Flash chromatography allowed the separation of the chiral isomers from the meso isomers. This very attractive synthesis was reported by Normant's groups [140], who resolved the racemic mixture with (+)-tartaric acid and obtained large amounts *R*, *R*-*N*, *N'*-dimethyl-1,2-diphenylethylenediamine (DMPEDA) 114.

The imidazolidines that result from the condensation of an aldehyde (ketones are much less reactive) with such a chiral diamine show the remarkable *C*<sub>2</sub> symmetry,



Scheme 6.72



Scheme 6.73

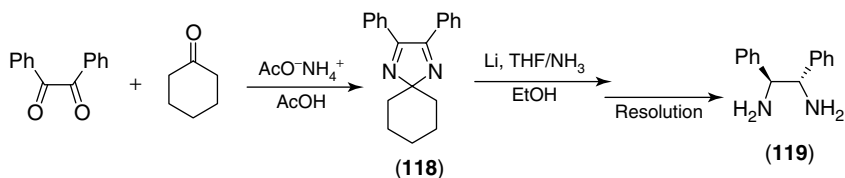
whose interest since the pioneering work by Kagan [141] is widely recognized [142]. In the present case, it should be noted that, in imidazolidine **115**, the created C-2 center is nonstereogenic and this avoids the necessity of controlling the stereochemistry of this center (as was the case with oxazolidines, see above). Alexakis and Mangeney took advantage of this fact when they developed the use of such amins as chiral auxiliaries for an impressive number of very original syntheses [143]. An example of such transformation is depicted in Scheme 6.72 [144].

Incidentally, Scheme 6.73 reveals another interesting feature: while condensation of glyoxal with 1,2-amino alcohols leads to a morpholine structure (see above) [17b], an analogous reaction leads to imidazolidines when 1,2-diamines come into play. Yet, both condensations involve iminium ions (**116** and **117**) as the key intermediate (Scheme 6.73), but its intramolecular cyclization affects either the C=N or the C=O bond according to the hydroxyl or amino nature of the nucleophile. To our knowledge, no explanation has been given to this opposite behavior.

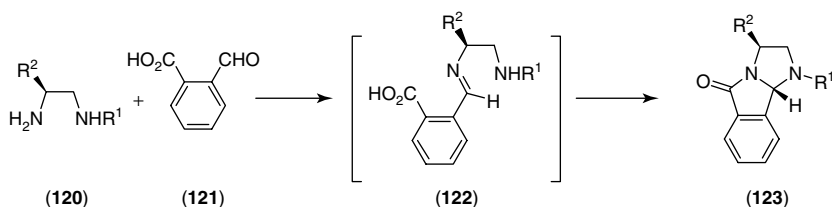
As mentioned above, enantiopure,  $C_2$ -symmetric 1,2-diamines are not simply available. Corey *et al.* [145] have described another way for their production. It consists in condensing benzil with cyclohexanone and reducing the formed bis-imine **118** as shown in Scheme 6.74; the enantiopure diamine **119** was then obtained via optical resolution with tartaric acid.

This method was taken up many a time afterwards [146]. In particular, Kanemasa and Onimura [147] made use of such diamines to prepare new chirality-controlling auxiliaries such as imidazolidine and made an exhaustive conformational analysis in order to understand their behavior during dipolar cycloadditions and Diels–Alder reactions.

Aiming to synthesize isoindolones, which present many interesting biological activities, Katritzki *et al.* [148] realized the ingenious transformation depicted in



Scheme 6.74



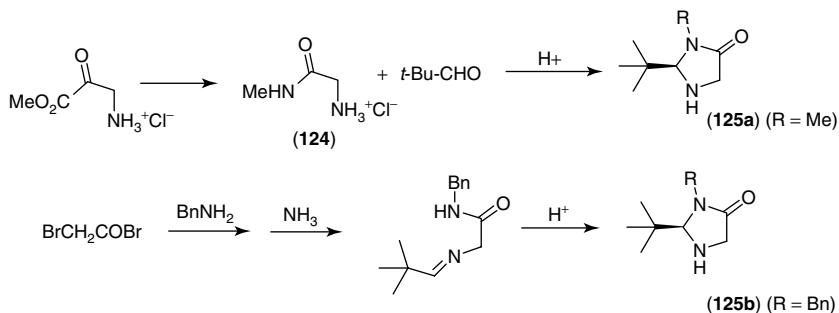
Scheme 6.75

Scheme 6.75. Condensation of enantiopure diamines **120** with 2-formylbenzoic acid **121** afforded, with both high yields and stereoselectivities, various tetrahydro-5H-imidazo[2,1-a]isoindol-5-one **123**. Imine **122** is a likely intermediate in which the addition of the amino moiety onto the imine bond occurs on the less crowded *re* diastereoface of the imine double bond.

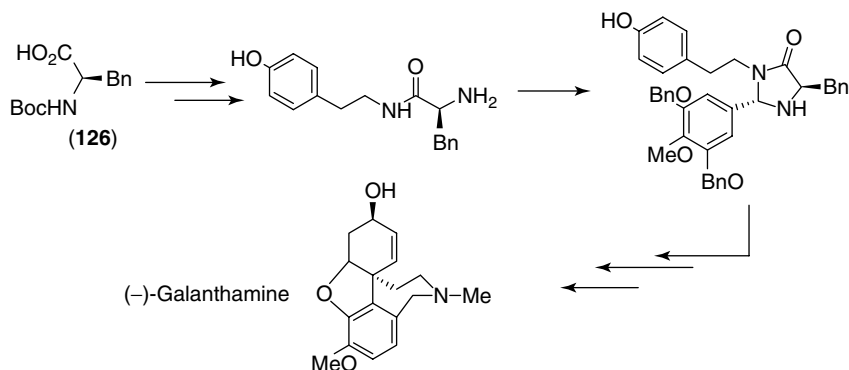
Actually, imidazolidine and imidazolidinone heterocycles take part in many fruitful ligands for various metal-catalyzed reactions or for organocatalyzed reactions [149].

#### 6.2.1.2 Imidazolidinones

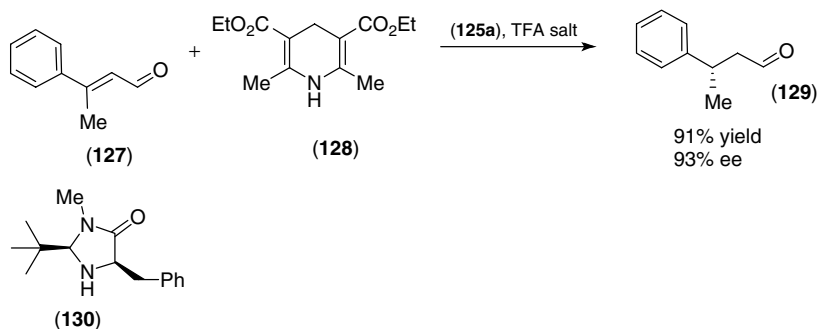
**4-Imidazolidinones** Lithium enolates of 4-imidazolidinones are the basis of the classical asymmetric transformation proposed by Seebach who founded the famous concept of “Self-generation of stereocenters” [150]. Imidazolidinones **125** were prepared in racemic form (Scheme 6.76) either by condensing the glycine-derived salt **124** with pivalaldehyde or via an indirect route from bromoacetyl bromide; mandelic acid was used in order to resolve the racemic mixtures and produce the



Scheme 6.76



Scheme 6.77



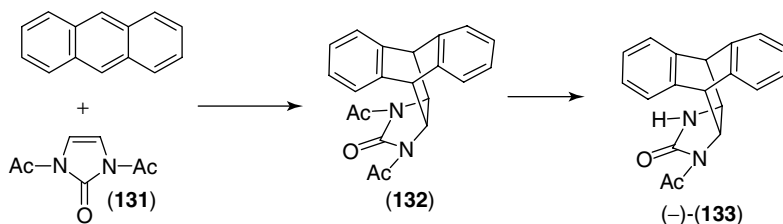
Scheme 6.78

enantiopure imidazolidinones [151]. Numerous other imidazolidinones were prepared in this way and these works mark out a new method for the enantioselective syntheses of many amino acids from such an asymmetric derivatization of glycine [152].

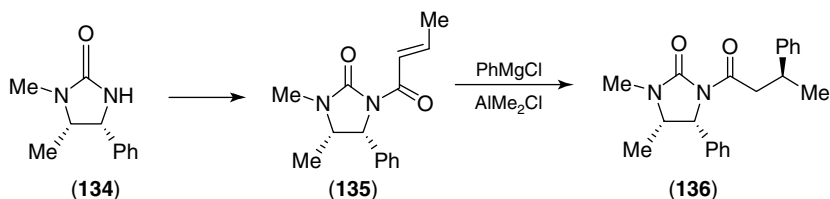
Clearly, every  $\alpha$ -amino acid, other than glycine, can be used, and in such a case the produced imidazolidinone shows one more stereocenter. In this fashion, the synthesis of (-)-galanthamine, performed by Node *et al.* [153], made use, as a starting material, of the imidazolidinone **126** formed from Boc-D-alanine (Scheme 6.77).

MacMillan recently introduced a new concept in the realm of organocatalysis: the lowest unfilled molecular orbital (LUMO) lowering iminium activation which has found many rewarding applications for various transformations [154]. For instance (Scheme 6.78), imidazolidine **125a** catalyzes an enantioselective transfer hydrogenation from Hantzsch ester **128**, and enal **127** was reduced to the optically active aldehyde **129**. Imidazolidinone **130** was also tested but the enantioselectivities thus obtained were lower than with **125a**.

An original route to chiral oxazolidin-2-ones has been described by Kunieda *et al.* [155] through the smooth cycloaddition of 1,3-diacetyl-2-imidazolone **131** and



Scheme 6.79



Scheme 6.80

anthracene (Scheme 6.79). This reaction leads to a meso adduct **132**, which was enantioselectively N-deacetylated by reaction with an enantiopure amino alcohol.

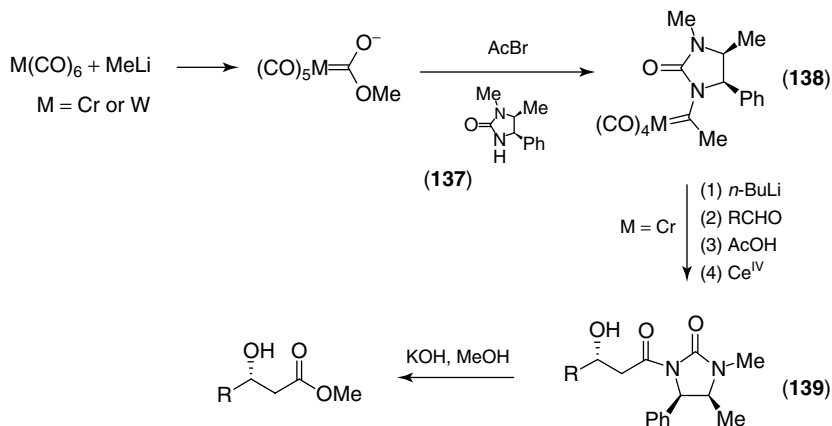
Compound **133** was used as an exceptionally rigid and congested chiral auxiliary for various asymmetric syntheses such as Diels–Alder reactions and enolate methylations [156].

**2-Imidazolidinones** 2-Imidazolidinone **134** is easily prepared following a Helmchen procedure [157] from ephedrine and urea. The chiral  $\alpha,\beta$ -unsaturated imide **135**, which was derived from the heterocycle **134**, was submitted (Scheme 6.80) to an asymmetric 1,4-addition in the presence of Lewis acids and this led to the formation of the adduct **136** [158].

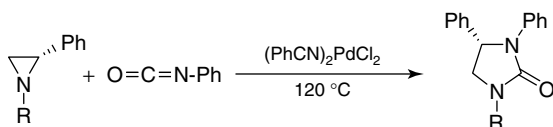
Another original application of a 4-imidazolidinone derivative in catalysis was found in the metallocarbene field. Complex **138**, which is formed from imidazolidinone **137** (Scheme 6.81), has been used for an original “aldol reaction” that affords the *N*-acyl imidazolidinone **139** with excellent stereoselectivity, as shown in Scheme 6.82 [159].

2-Imidazolidinones can also be prepared from an original cycloaddition to phenyl isocyanate [160]. As a matter of fact, Alper reported (Scheme 6.82) that this isocyanate adds to (*S*)-(+)-*n*-butyl-2-phenylaziridine in the presence of a Pd<sup>II</sup> catalyst. It is worth noting that the configuration of the aziridine stereogenic center is retained during this process.

It can be concluded that, owing to their straightforward availability, imidazolidines as well as imidazolidinones play an important role in the asymmetric synthesis as chiral auxiliaries, a field whose expansion has been at lightning speed. However, it seems that their use as chiral ligands in metal-catalyzed reactions or as organocatalysts constitutes at the present time a major subject of research in this area.



Scheme 6.81



Scheme 6.82

## 6.2.2

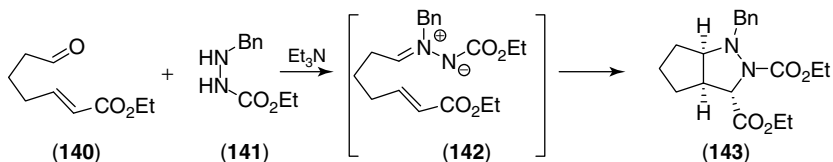
## Pyrazolidines and Pyrazolines

## 6.2.2.1 Pyrazolidines

As was commonly observed in this series, pyrazolidines exhibit very interesting biological properties [161]. On the other hand, from a purely chemical point of view, chiral pyrazolidines can be used for the synthesis of optically active 1,3-diamines by the N–N bond cleavage [162].

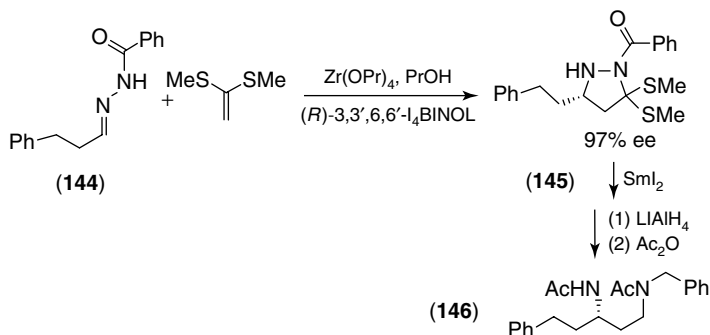
Here again, as in the aforementioned case of oxazines, most synthetic methods resort to dipolar cycloadditions to various dipolarophiles. For instance, the azomethine imine dipole **142** is an intermediate during the totally regio- and diastereoselective reaction (Scheme 6.83) of the substituted hydrazine **141** to the substrate **140**, which gave pyrazolidine **143** [163].

Kobayashi *et al.* described an enantioselective approach to such structures. They made use of a chiral zirconium catalyst to perform the [3 + 2] cycloaddition of

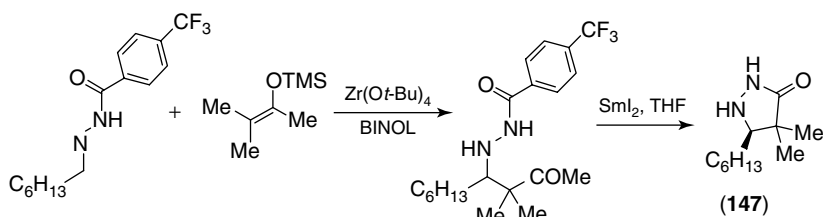


Scheme 6.83

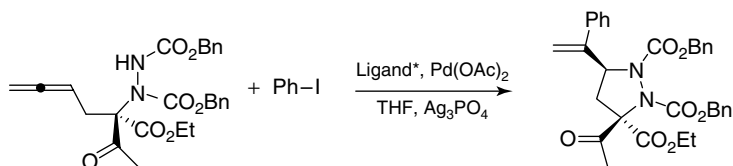




Scheme 6.84



Scheme 6.85

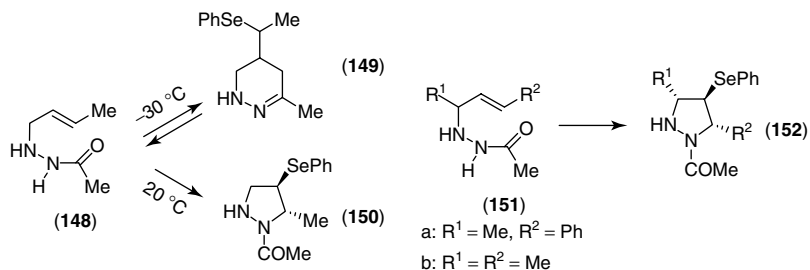


Scheme 6.86

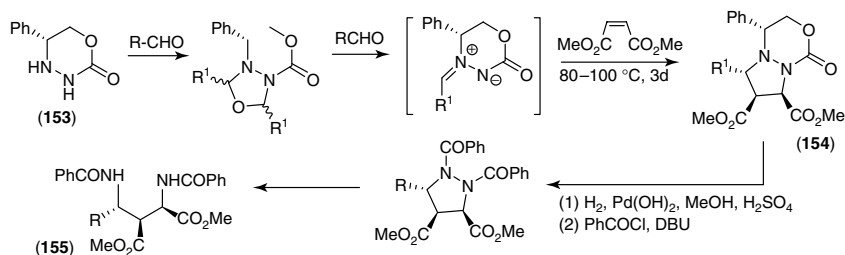
acylhydrazones onto achiral substrates (Scheme 6.84). With tetraiodo- $(R)$ -4-bina-phtol (BINOL) as the enantiopure ligand, they were able to synthesize, for instance, pyrazolidine **145**, whose N–N bond cleavage mediated by  $\text{SmI}_2$  allowed the formation of the diamino compound **146** [164]. The observed enantioselectivity enabled the authors to discard a possible stepwise pathway in favor of a concerted one.

Acylhydrazones were also used [165] as imine equivalents during a chiral-zirconium-catalyzed Mannich-type reaction (Scheme 6.85). Here again, a BINOL derivative (3,3'-BrBINOL) was chosen as the chiral ligand. The produced hydrazide treated by  $\text{SmI}_2$  eventually gave pyrazolidine **147**.

In the same way, a palladium-based chiral catalyst was reported to allow the cyclization between optically active allenyl hydrazines and organic halides: that is, with a double asymmetric induction process (Scheme 6.86). Many asymmetric ligands were tested, and finally the  $(R, R)$ -box ligand **ent-43** ( $R = \text{Bn}$ ) gave the best results [166].



Scheme 6.87



Scheme 6.88

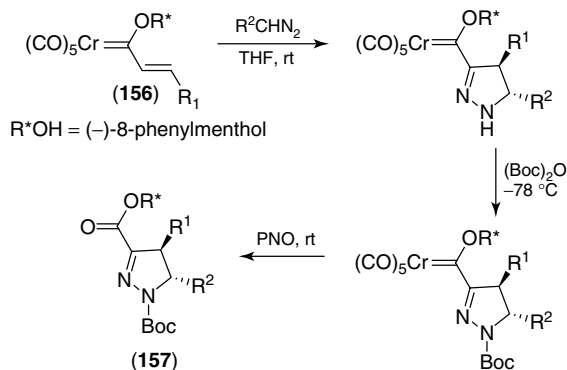
Organoselenium-induced intramolecular cyclization of *N*-allyl acetylhydrazide **148** affords either oxadiazine **149** or pyrazolidine **150** (Scheme 6.87). It was shown that the five-membered heterocycle was the result of a thermodynamic control, whereas its six-membered isomer was formed under kinetically controlled conditions. Interestingly, substrates **151a–b** were cyclized to produce compounds **152a–b** as the sole diastereomers [167].

Husson *et al.* [162, 168] described the formation of pyrazolidines **154** via a tandem process from carbazate **153**. The last step in Scheme 6.88 involves a cycloreversion–cycloaddition process; various dipolarophiles (methyl maleate, fumarate and crotonate) were successfully employed. A chemoselective electroreduction of the functionalized pyrazolidines allowed the synthesis of enantiopure 1,3-diamines such as **155**, which was obtained when dimethyl maleate was chosen as the dipolarophile.

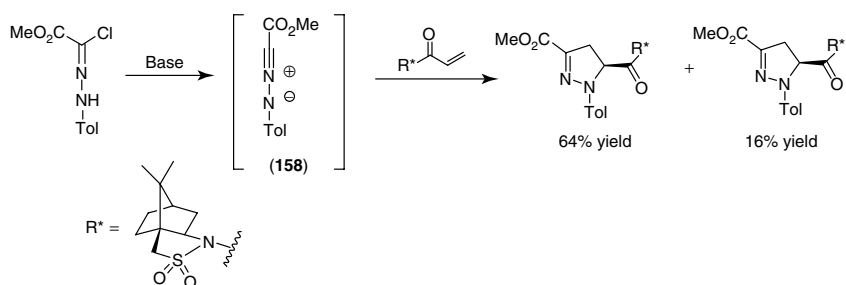
Carreira [169] described the asymmetric synthesis of  $\Delta^2$ -pyrazolines **157** from dipolar cycloaddition reaction of trimethylsilyl diazomethane and camphorsultam-derived acrylates and showed afterwards that various Lewis acid-catalyzed additions to these pyrazolines afforded very smoothly the corresponding pyrazolidines.  $\text{TiCl}_4$  proved to be the optimal Lewis acid and the adducts were isolated in many cases as single diastereomers.

#### 6.2.2.2 Pyrazolines

The preceding report initiates here a section devoted to the synthesis of chiral pyrazolines. In the field of the scarcely explored dipolar cycloadditions with metal carbene complexes, Barluenga and coworkers [170] described the reaction of



Scheme 6.89

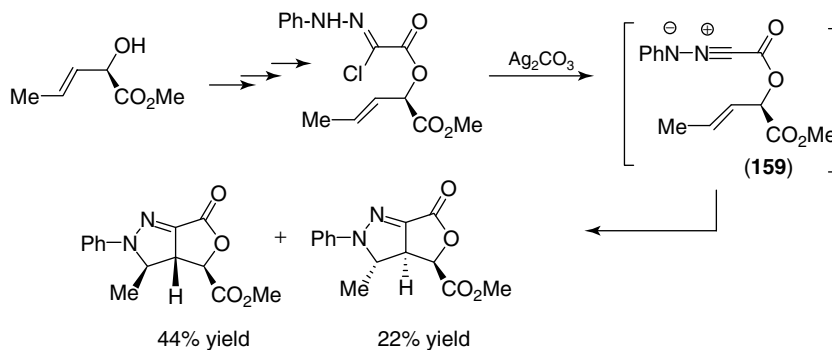


Scheme 6.90

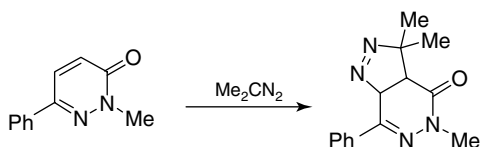
diazo compounds with alkenyl Fischer carbenes **156** derived from chiral alcohols (Scheme 6.89). In this way, enantiopure  $\Delta^2$ -pyrazolines **157** were obtained.

The process displayed in Scheme 6.89 can be still improved because the formation of  $\Delta^2$ -pyrazolines **157** can be performed in a one-pot reaction. It is worth noting that stereoselectivity was excellent, whereas an analogous reaction from menthyl *trans*-cinnamate alone (that is, the ligand linked to Cr in **156**) showed a much lesser stereoselectivity when directly condensed with  $\text{TMSCHN}_2$ . Barluenga also showed that treatment of such pyrazolines with  $\text{LiBEt}_3\text{H}$  leads to pyrazolidines (see above). Barluenga also described a similar reaction in which metal carbene complexes reacted with nitrile oxides; however, in this case, the stereoselectivity was not so high as in the preceding case [171]. Apart from this single use,  $\Delta^2$ -pyrazolines were examined for their physical applications [172a] and their pharmacological activity [172b].

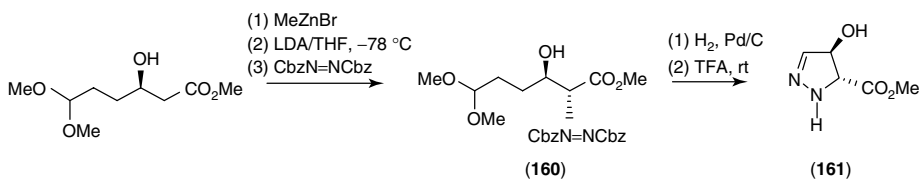
Cycloadditions with nitrile imine intermediates **158** were studied by Molteni *et al.* (Scheme 6.90), who tested various chiral auxiliaries  $\text{R}^*$  in such condensations [173]. Intramolecular cycloadditions with nitrile imine intermediates **159** were also described [174], but in this case too the stereoselectivity was rather poor as shown in Scheme 6.91; however, the resulting diastereomers can be easily separated through column chromatography and appeared to be enantiomerically pure.



Scheme 6.91



Scheme 6.92



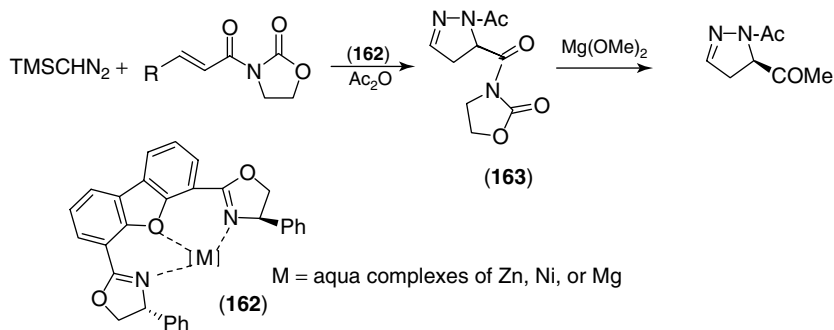
Scheme 6.93

Actually, it was already shown by Stanovnick and Svete [175] that dipolarophiles can be the substrates of such cycloaddition: Scheme 6.92 displays one example of such reaction with diazomethane as the dipolar constituent.

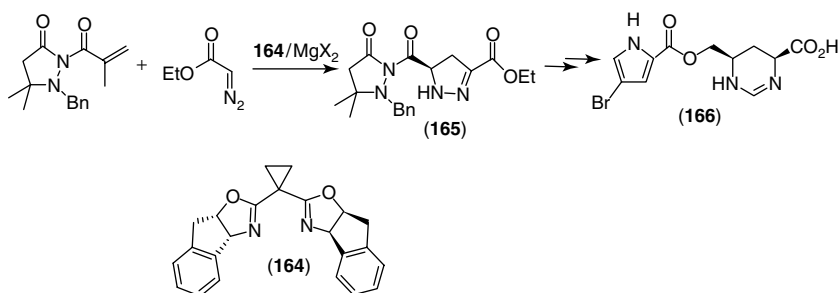
Another intramolecular cycloaddition leading to  $\Delta^2$ -pyrazolines **161** was described by Genet and Greck [176]. The hyrazino derivative **160** was first obtained (Scheme 6.93) from the zinc enolate of the hydroxyester by treatment with dibenzylazodicarboxylate, and it was then N-deprotected and cyclized in the presence of trifluoroacetic acid.

A cooperative chirality control was observed by Kanemasa [177] during a Lewis acid-catalyzed cycloaddition of a diazoalkane (Scheme 6.94). Thus, several chiral catalysts were screened, and ligand **162** was found to be the most effective to perform the cycloaddition that led to  $\Delta^2$ -pyrazolines **163** with excellent yields and enantioselectivity.

Unsaturated pyrazolidinone imides, though less reactive than the usual dipolarophiles, were found to be efficient substrates for cycloadditions involving diazoacetates [178]. The produced pyrazoline **165** was obtained in an enantiopure form, and Sibi took advantage of this reaction in order to synthesize (–)-manzazidin



Scheme 6.94



Scheme 6.95

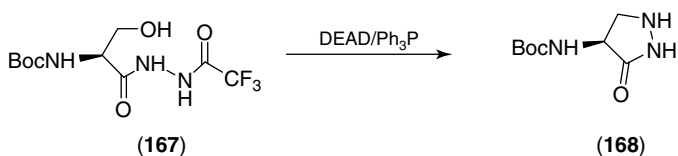
A **166** (Scheme 6.95). In this case, as in many others reviewed above, a chiral Box ligand **164** was used in the catalyst system.

### 6.2.3

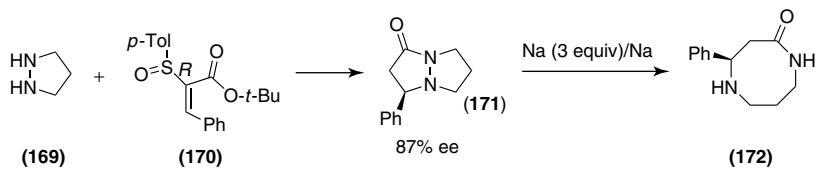
#### Pyrazolidinones

One of the first preparations of a chiral pyrazolidinone was performed by Elly's group [179]; it concerns compound **168**, a key intermediate for the synthesis of carbapenem analogs that have useful antibacterial properties [180]. The Mitsunobu reaction (Scheme 6.96) applied to the serine-derivative **167** allowed the preparation of large quantities of pyrazolidinone **168**.

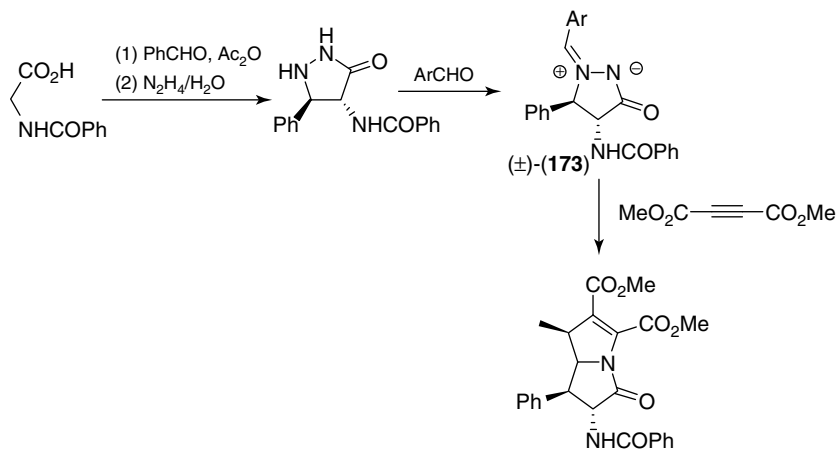
An interesting synthesis was described by Matsuyama [181], who showed that the conjugate addition of pyrazolidine **169** to optically active vinylsulfoxide **170** led to



Scheme 6.96



Scheme 6.97



Scheme 6.98

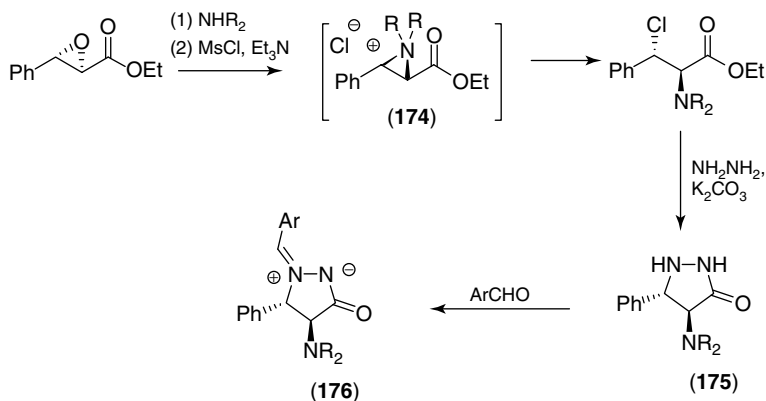
pyrazolidinone **171** with a high level of enantioselectivity (Scheme 6.97). Breaking the N–N bond with Na/NH<sub>3</sub> furnishes diazacyclooctanone **172**.

Another strategy was used by Svete's group [182]; however, this method affords pyrazolidinones but only as racemic mixtures. Scheme 6.98 depicts this process, which furnishes an heterocycle that can be conveniently transformed into azomethine imine **173**. This dipole reagent is clearly very reactive toward various cycloadditions; one of these reactions with dimethylacetylenedicarboxylate is illustrated here.

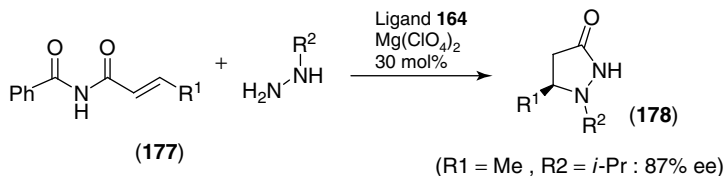
Actually, the fact that pyrazolidinones can be easily transformed into such dipolar reagents is known from the pioneering work by Dorn [183], and Oppolzer already made use of the resourceful reactivity of azomethine imines [184].

Sharpless [185] described a versatile access to these heterocycles from an enantiopure oxirane as shown in Scheme 6.99, improving greatly the above-reported Svete's approach since nonracemic compounds are now obtained. Transformation of the oxirane into the aziridinium structure **174** is the key step of this process, and it should be noted that pyrazolidinone **175** could be converted into azomethines **176** which were used as starting materials for cycloadditions leading to more complex pyrazolidinones.

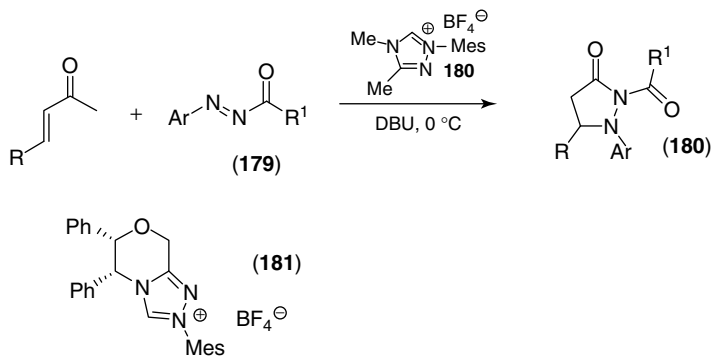
During his studies on the effect of pyrazolidinones as chiral templates on the reactivity and selectivity of many enantioselective reactions [186], Sibi described recently [187] the condensation of benzylhydrazine **177** to various benzimides **178**



Scheme 6.99



Scheme 6.100



Scheme 6.101

in the presence of a catalytic system composed by a Lewis acid linked to the Box ligand **164** (Scheme 6.100). In this way, many pyrazolidinones (for instance **179**) were stereoselectively obtained.

A new method that looks very promising has been described by Chan and Scheidt [188]. The heterocyclic carbene derived from the triazolium salt is an excellent catalyst for a completely regioselective cycloaddition (Scheme 6.101) between enones and acaryldiazenes **179** in order to produce various pyrazolidinones **180**.

Moreover, these authors reported also that the chiral carbene formed from the triazolium salt **181** produces enantioselectively pyrazolidinones. The mechanism of

these transformations involves the addition of the carbene to the  $\alpha$ ,  $\beta$ -unsaturated aldehyde to give a homoenolate intermediate, which then undergoes a formal [3 + 2] cycloaddition with the diazene.

### 6.3

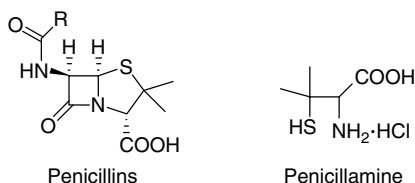
#### Five-Membered Heterocycles with N and S Atoms

##### 6.3.1

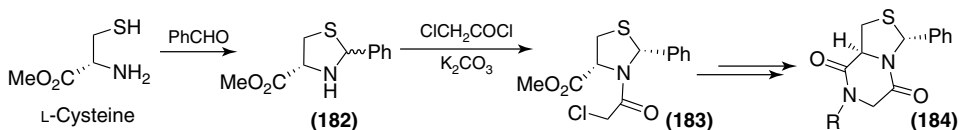
##### Thiazolidines

Thiazolidines have received particular attention owing to their pharmacological activity. Among the large number of compounds containing a thiazolidine ring, penicillins are the most popular ones (Scheme 6.102). The thiazolidine ring in these structures was commonly introduced from D-penicillamine hydrochloride, which was cyclized in the presence of an aldehyde [189]. In this manner, a countless number of penicillin derivatives have been prepared [190].

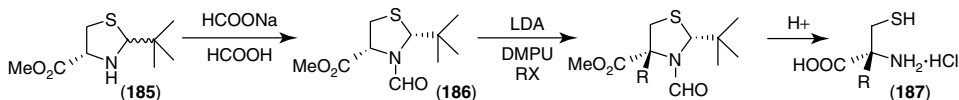
L-Cysteine (and 1,2-aminothiols in general) reacts with simple aromatic aldehydes in a nonstereoselective way to produce mixtures of the two epimers at C-2. Under specific conditions, N-acetylation of the diastereoisomeric mixture leads to either 2-4-*cis*- or 2-4-*trans*-2-aryl-3-acetyl-1,3-thiazolidine-4-carboxylic acids [191]. For instance, the acylation of a diastereoisomeric mixture of (2*S*, 4*R*) and (2*R*, 4*R*)-2-phenyl-4-carbomethoxy-1,3-thiazolidine with chloroacetylchloride in the presence of potassium carbonate led to the selective formation of the *cis* isomer **183** [192], which was used to synthesize the chiral thiazolopyrazine **184** (Scheme 6.103).



Scheme 6.102



Scheme 6.103



Scheme 6.104



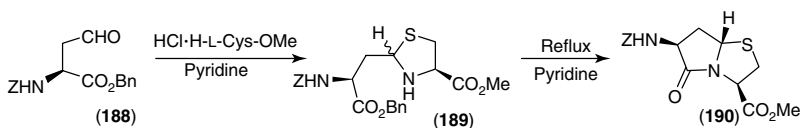
N-Formylation of the thiazolidine **185**, derived from (*R*)-cysteine methyl ester hydrochloride and pivalaldehyde, led only to the syn diastereoisomer of the compound **186**. Alkylation of compound **186** in a basic medium with alkyl bromide occurred exclusively anti to the bulky *t*-butyl substituent (Scheme 6.104). This method was applied to the synthesis of enantiopure 2-alkyl cysteines **187** [193].

Baldwin and coworkers [194] synthesized several  $\gamma$ -lactam analogs of penems possessing antibacterial activity (Scheme 6.105). Condensation of aspartic acid semialdehyde with L-cysteine methyl ester **188** in pyridine afforded a 1:1 mixture of the diastereoisomeric thiazolidines **189**, which was refluxed in pyridine to give the bicyclic lactam **190** (45% yield).

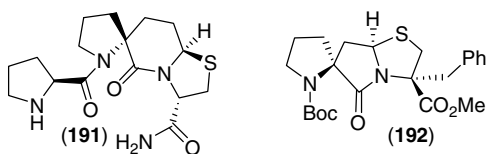
An analogous approach was reported to synthesize spiro bicyclic thiazolidine lactams **191** [195] and **192** [196] (Scheme 6.106), which are  $\beta$ -turn mimetics and therefore valuable tools in order to study the bioactive conformation of biologically active peptides.

Geyer and Moser [197] prepared the first bicyclic peptidomimetic, the thiazolidine lactam **195** derived from the carbohydrate precursor **193** (Scheme 6.107). After deprotection, the amino group of **195** was elongated with a glycine derivative.

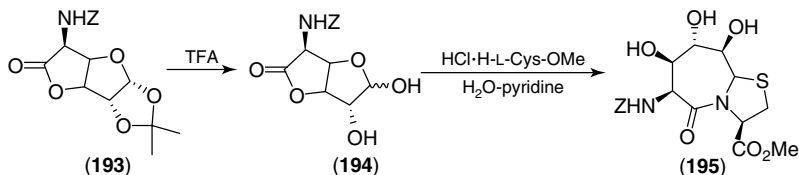
Several chiral catalysts containing a thiazolidine ring have been reported [198]. Natural L-cysteine and derivatives were often used in this way. For example, chiral thiazolidines were easily prepared from the condensation of L-cysteine ester with aldehydes or ketones; they were used as starting materials for the synthesis of a wide range of ligands **196**, which catalyzed an enantioselective addition of diethylzinc to aldehydes [199] and an arylation of aldehydes using aryl boronic acids [200], as shown in Scheme 6.108.



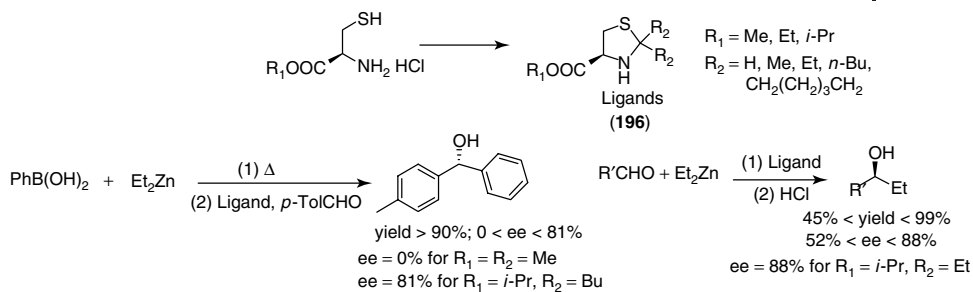
Scheme 6.105



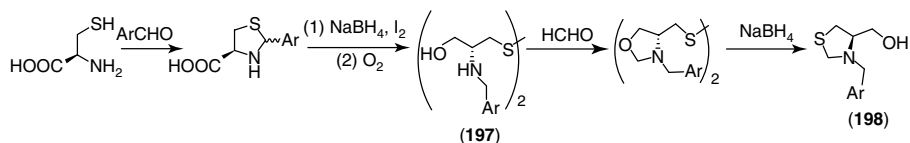
Scheme 6.106



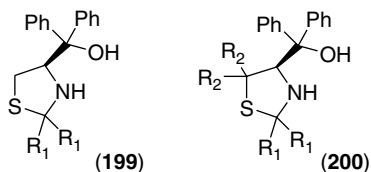
Scheme 6.107



Scheme 6.108



Scheme 6.109



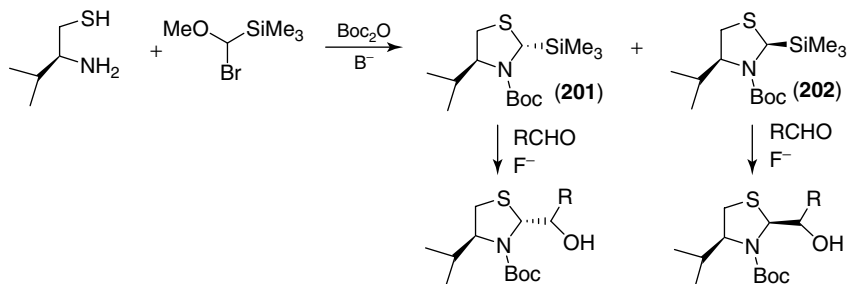
Scheme 6.110

From these works, it appears that the thiazolidine derivatives have higher enantioselectivity when they have a larger steric bulk in the thiazolidine rings.

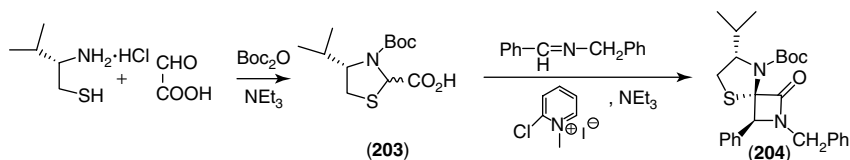
Braga *et al.* [201] synthesized the new thiazolidine ligand **198** derived from disulfide **197**, obtained in an easy three-step synthesis from L-cysteine, as described in Scheme 6.109. This ligand was used in asymmetric palladium-catalyzed allylations and provided the allylation product in high yield and with high enantiomeric excess (80%).

The chiral 2,2-disubstituted thiaprolinol derivatives **199** [202] and **200** [203] were used as ligands for diethylzinc addition to aldehydes and for borane reduction of aromatic ketones. These catalysts led to alcohols with moderate to good enantioselectivities (Scheme 6.110).

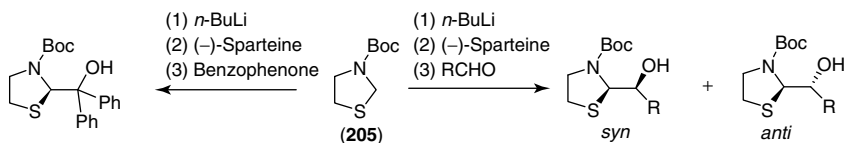
Thiazolidines were also used as new chiral formyl anion equivalents. Several silylated thiazolidines were synthesized, generally as a mixture of the *cis* and *trans* diastereoisomers **201** and **202**, which could be separated by chromatography to give enantiopure compounds [204]. Diastereoselectivity was not observed during the reaction with aldehydes in the presence of fluoride ion; however, functionalization occurred with a total retention of configuration of the starting C–Si bond (Scheme 6.111).



Scheme 6.111



Scheme 6.112

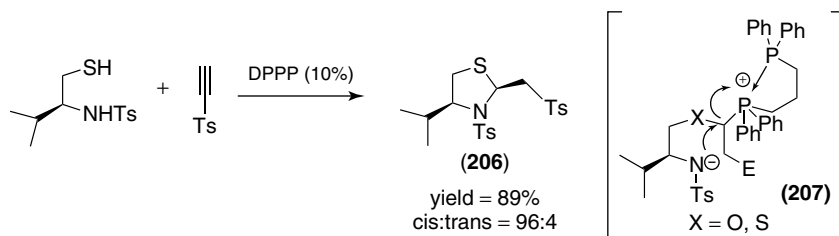


Scheme 6.113

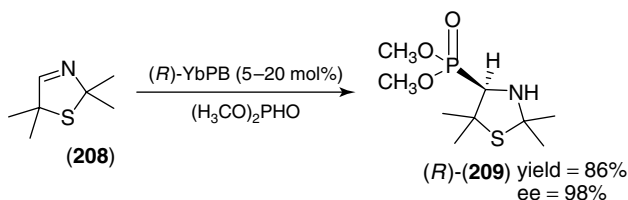
A Staudinger reaction between chiral ketenes and imines was reported to afford enantiopure spiro- $\beta$ -lactams derived from 1,3-thiazolidines [205]. The best result, as regards diastereoselectivity, was obtained with the 4-*iso*-propyl-1,3-thiazolidine-2-carboxylic acid **203**, which led to only one enantiomerically pure spiro- $\beta$ -lactam **204** in 46% yield (Scheme 6.112). The authors stressed the importance of the C-4 substitution of the thiazolidine ring on the stereochemical outcome of this reaction.

Toru and coworkers used the simple N-Boc-thiazolidine **205** as a formyl anion equivalent [206]. As shown in Scheme 6.113, the reaction of the lithiated **205** with benzophenone in the presence of  $(-)$ -sparteine afforded the products with up to 93% ee. This reaction was expanded to various aromatic and aliphatic aldehydes to afford the products of addition with high enantioselectivity but moderate diastereoselectivity (syn/anti = 55/45).

Recently, Kwon and coworkers [207] prepared functionalized thiazolidines and oxazolidines with a high yield, one-step biphosphine-catalyzed mixed double-Michael reaction. Diphenylphosphinopentane (DPPP) was the best catalyst used for this reaction compared to diphenylphosphinomethane (DPPM), diphenylphosphinoethane (DPPE), and diphenylphosphonobutane (DPPB). The importance of the tether length between the two phosphine moieties was explained by invoking the stabilization of the intermediate phosphonium ion **207**, as represented in Scheme 6.114.



Scheme 6.114

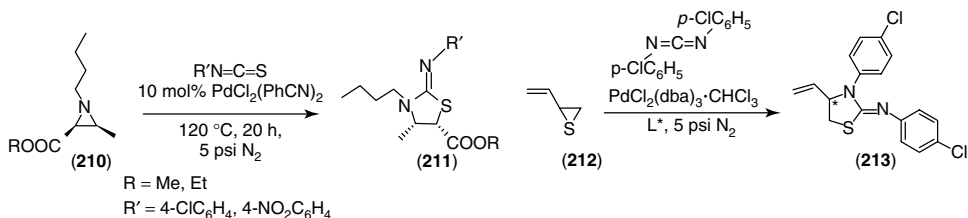


Scheme 6.115

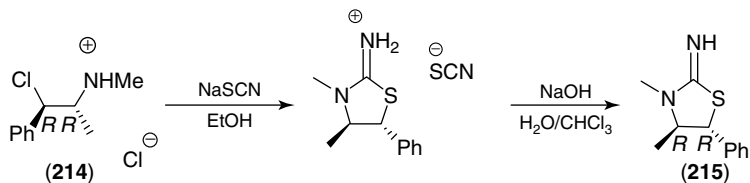
An efficient enantioselective approach to the pharmaceutically interesting 4-thiazolidinephosphonate (*R*)-**209** was described [208] using 2,2,5,5-tetramethyl-3-thiazoline **208** and various heterobimetallic lanthanoid catalysts (Scheme 6.115). The best results were obtained with (*R*)-YbKB as catalyst (where B = (*R*)-(+)-binaphthol).

#### 6.3.1.1 Iminothiazolidines

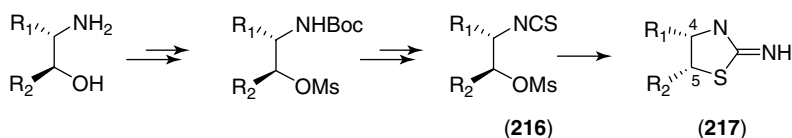
Being present in a large variety of biologically active compounds, 2-iminothiazolidines have been intensively studied [209]. Ring expansion of aziridines, which leads to five-membered heterocycles, appears to be a powerful tool for the construction of iminothiazolidines. Palladium-catalyzed ring expansions of aziridines have thus been described by Alper *et al.*, who reported an enantioselective version of this reaction (Scheme 6.116) [210]. Treatment of aziridines **210** with isocyanates in the presence of bis(acetonitrile)palladium dichloride afforded thiazolidines **211** in both regio- and stereoselective manner. The enantioselectivity of the palladium-catalyzed cycloaddition was unequivocally demonstrated; consequently, the relative and absolute stereochemistry was conserved throughout this cycloaddition reaction. An analogous ring expansion of thiiranes with carbodiimide catalyzed



Scheme 6.116



Scheme 6.117



Scheme 6.118

by palladium with 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP)-type ligands afforded iminothiazolidines **213** in good yields (up to 68% ee) [211].

The ephedrine derivative **214** was converted into a 2-iminium derivative upon treatment with sodium thiocyanate. This salt was neutralized and gave the enantiopure 2-iminothiazolidine **215**, preserving the relative and absolute configuration of the starting material (Scheme 6.117) [212].

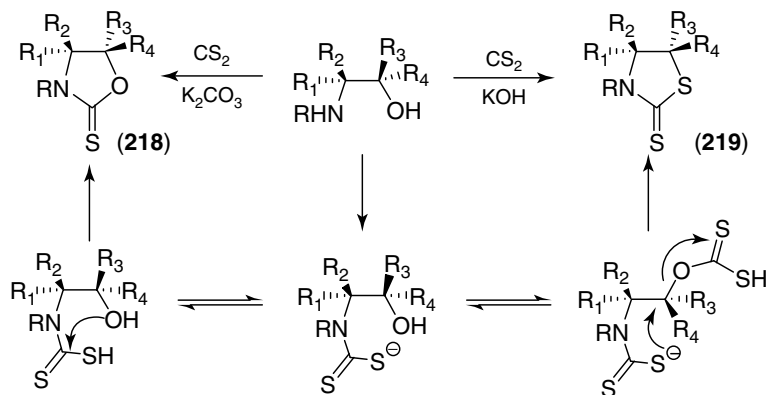
Enantiopure 4,5-dialkyl-2-imino-1,3-thiazolidines have been synthesized from commercially available  $\beta$ -amino alcohols or  $\beta$ -amino acids. The cyclization of the resulting isothiocyanates **216** was performed in the presence of ammonia and it occurred with inversion of configuration at C-5 [213]. The compounds **217** are potent inducible nitric oxide (NO) synthase inhibitors (Scheme 6.118).

### 6.3.1.2 Thiazolidinethiones

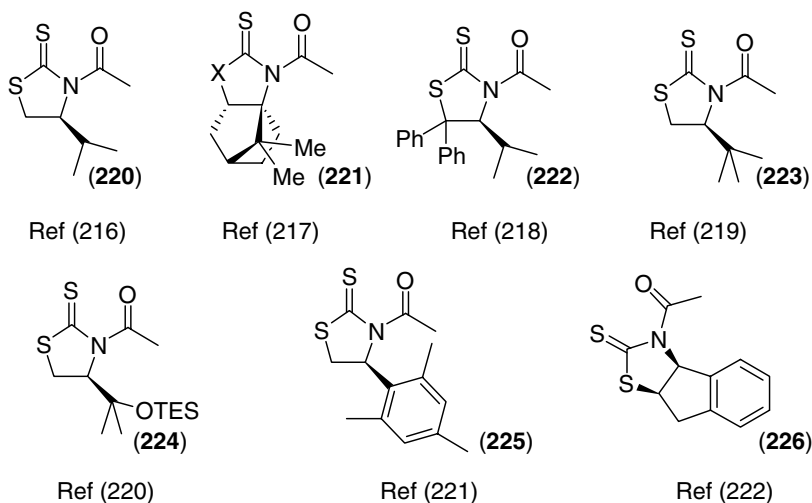
Chiral thiazolidinethiones constitute a class of versatile auxiliaries for asymmetric synthesis [214]. They are easily synthesized from  $\beta$ -amino alcohols and carbon disulfide in a basic medium.

Le Corre and coworkers [215] studied the reaction between amino alcohols and carbon disulfide. According to the experimental conditions, either oxazolidinethiones **218** or thiazolidinethiones **219** could be obtained. The authors reported that the preparation of oxazolidinethiones required mild conditions, whereas thiazolidinethiones were isolated under more drastic conditions (excess of  $\text{CS}_2$ , very alkaline KOH medium and long reaction time). The formation of thiazolidinethiones occurred with an inversion of configuration of the oxygen-bearing carbon, as depicted in Scheme 6.119.

Thiazolidinethiones have been used in a wide variety of transformations, mainly for the asymmetric aldol condensation, but also in order to differentiate the enantiotopic groups in molecules bearing prochiral centers and for other applications. All the thiazolidinethiones **220–226** depicted in the Scheme 6.120 undergo highly efficient and selective aldol condensation.



Scheme 6.119

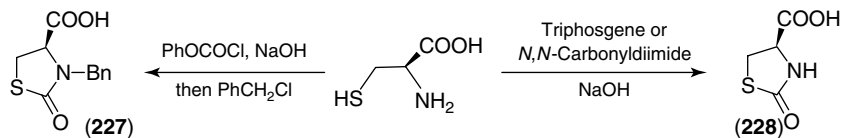


Scheme 6.120

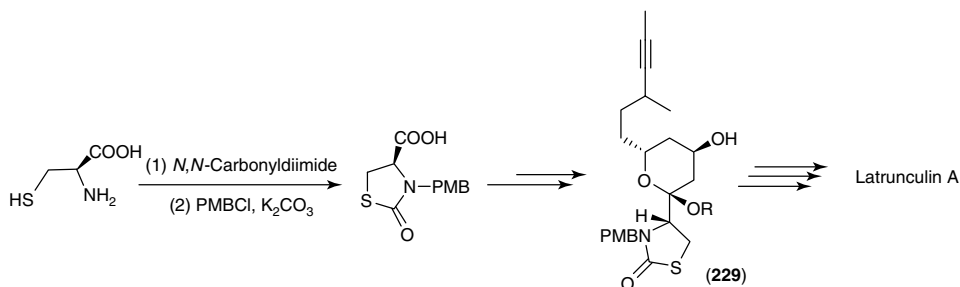
### 6.3.1.3 Thiazolidinones

Thiazolidinones (carbonyl group located at position C-2, C-4 or C-5) have received much attention, owing to their uses as intermediates and to their diverse biological activities [223, 224].

Reaction between L-cysteine and N, N-carbonyldiimidazole [225] or triphosgene [226] afforded the corresponding thiazolidin-2-one. In a practical synthesis of (+)-biotin, Seki *et al.* reported a one-pot preparation of N-benzyl-2-thiazolidinone-4-carboxylic acid **228** from L-cysteine. Treatment with phenyl chloroformate and NaOH, followed by reaction with benzyl chloride, afforded product **227** in high yield [227] (Scheme 6.121).



Scheme 6.121



Scheme 6.122

Compound **229**, possessing a thiazolidine moiety, is a key building block for the synthesis of latrunculin A. It was synthesized from cysteine in a classical way (Scheme 6.122) [228].

### 6.3.2

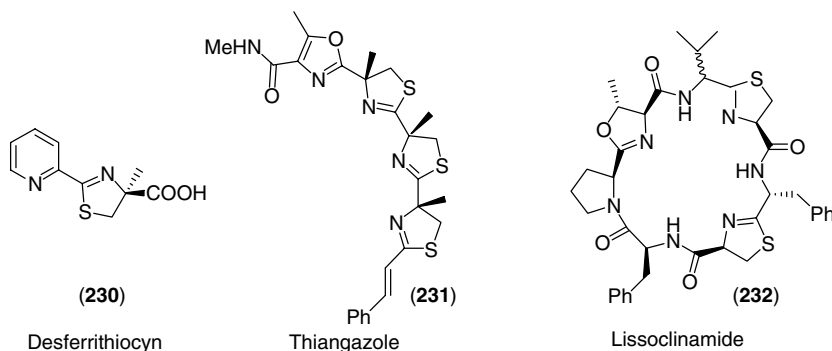
#### Thiazolines

##### 6.3.2.1 2-Thiazolines

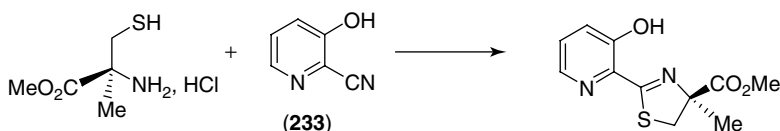
Chiral thiazolines are mainly known as subunits of biologically active macromolecules, which exhibit antitumor and anti-HIV activities, but they are less familiar than their oxygenated analogs, namely the oxazolines. As a matter of fact, the 2-aminothiols, which can be viewed as the most obvious precursors, are not easily available compared to the corresponding amino alcohols. Nevertheless, the asymmetric synthesis of thiazolines has received renewed attention because thiazolines and bis-thiazolines have been proved to possess great potential as a new class of ligands in enantioselective synthesis.

Until 1990, desferrithiocyn **230**, a natural ferric ion chelator isolated from *Streptomyces antibioticus*, was the only example of a naturally occurring 4-methyl substituted  $\Delta^2$ -thiazoline; since then, a very wide range of new and biologically active linear and cyclic peptides containing at least one thiazoline ring have been isolated and characterized. For example, thiangazole B **231**, isolated from blue green algae, is a linear, fused 2,4-disubstituted poly-thiazoline/oxazole ring, and lissoclinamide **232** is a marine cyclopeptide alkaloid with two thiazolidine rings, as shown in Scheme 6.123.

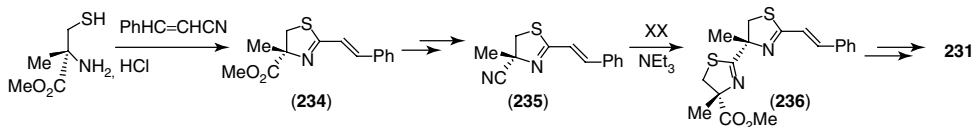
In structures **230** and **231**, the thiazoline rings are derived from 2-methylcysteine, and different authors have developed different strategies for the elaboration of this thiazoline ring. With the aim of synthesizing desferrithiocyn, Pattenden



Scheme 6.123



Scheme 6.124



Scheme 6.125

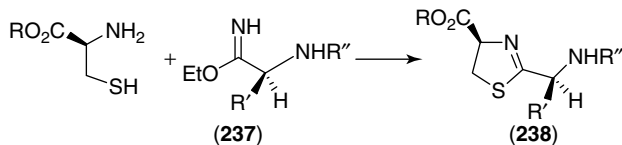
and coworkers elaborated first the thiazoline ring from the hydrochloride of (S)-(2)-methylcysteine methyl ester [193], which reacted with the pyridine nitrile derivative **233** to give the (S)-desferrithiocyn **230** in high yield (Scheme 6.124).

To synthesize thiagazole, the same authors synthesized the thiazoline ring as described above. The resulting ester **234** was converted into the nitrile **235**, and a second cyclocondensation reaction produced the bis-thiazoline **236** as shown in the Scheme 6.125 [229].

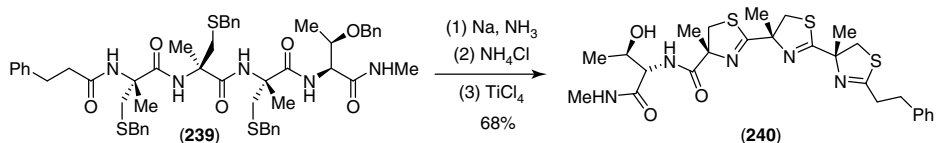
Thiazolines containing amino acids **238** could be obtained efficiently in an optically pure form from simple condensation reactions between cysteine derivatives and N-protected imino ethers **237**, which are derived from natural amino acids (Scheme 6.126) [230].

Chiral centers attached to the C-2 position of thiazolines are prone to epimerization; therefore racemization-free methods have been developed. The Mitsunobu reaction [231a] or treatment with Burgess' reagent (methyl N-(triethylammonio-sulfonyl)carbamate) [231b] applied to thiopeptides were efficiently used to introduce thiazolines in the peptide backbone and proceeded without loss of stereochemical integrity.

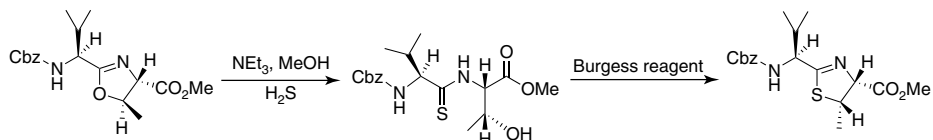




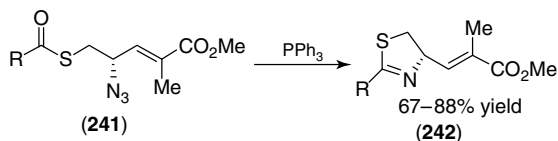
Scheme 6.126



Scheme 6.127



Scheme 6.128



Scheme 6.129

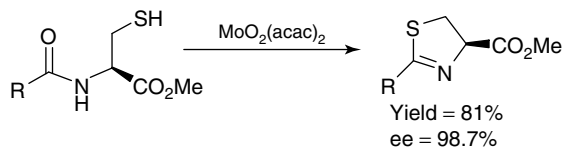
As shown in Scheme 6.127, Heathcock and Parsons [232] made use of the tetrapeptide **239** that was reductively debenzylated and was cyclized by treatment with TiCl<sub>4</sub> in order to provide the tris-thiazoline **240**, a precursor of thangazole **231**.

Wipf and coworkers [233] used also Burgess' reagent in a general method for the oxazoline–thiazoline conversion. This reaction was stereoselective and essentially free of racemization (Scheme 6.128).

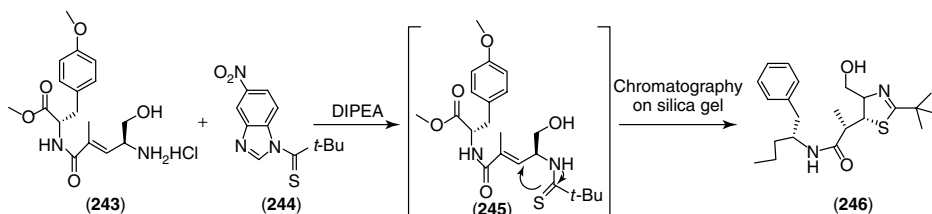
A one-pot Staudinger reduction/aza-Wittig reaction was used as a mild and versatile process for the conversion of azido-thiolesters **241** into enantiopure 2,4-disubstituted thiazolines **242** (Scheme 6.129) [234].

Recently, the dehydrative cyclization of *N*-acylcysteine derivatives was carried out in the presence of a molybdenum oxide catalyst to afford thiazolines in high yield, as shown in Scheme 6.130 [235].

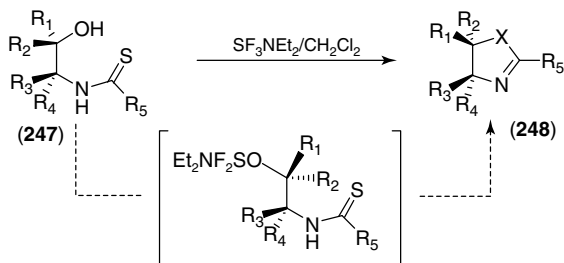
Xu and Ye [236] used amino alcohols to synthesize 2,4,5-trisubstituted thiazolines **246** with high diastereoselectivity via the intramolecular conjugate reaction described in Scheme 6.131. The unstable intermediate thioamide **245** readily undergoes an intramolecular conjugate addition reaction in a weak acidic medium (silica gel).



Scheme 6.130



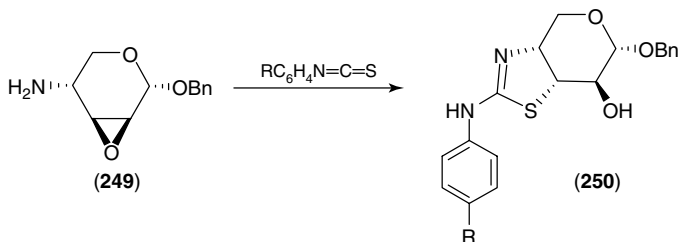
Scheme 6.131



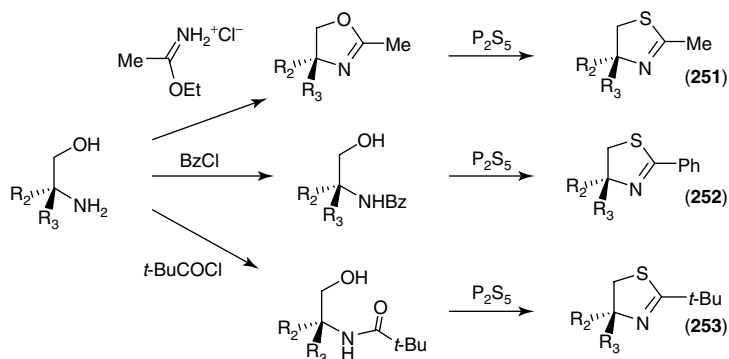
Scheme 6.132

Diethylamidodisulfur trifluoride (DAST) was used as a powerful hydroxyl activating agent for the intramolecular cyclization of (1,2)-thioamidoalcohols to 2-thiazolines, as shown in Scheme 6.132; this reaction was totally diastereoselective with the inversion of configuration at C-5 [237].

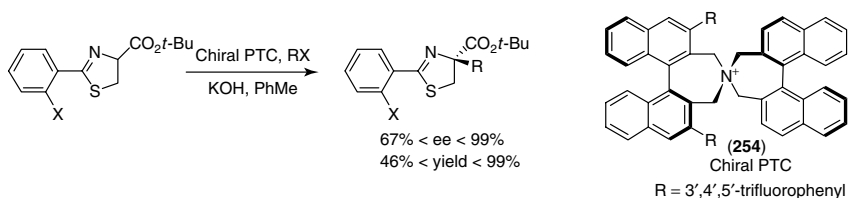
The amino sugar **249** was allowed to react with para-substituted phenyl isothiocyanates, and thiazoline derivatives **250** were thus obtained (Scheme 6.133) [238].



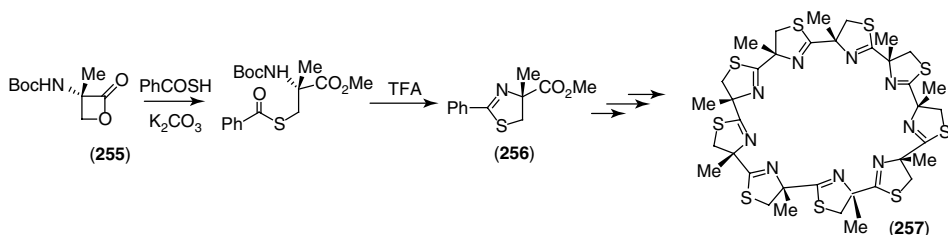
Scheme 6.133



Scheme 6.134



Scheme 6.135

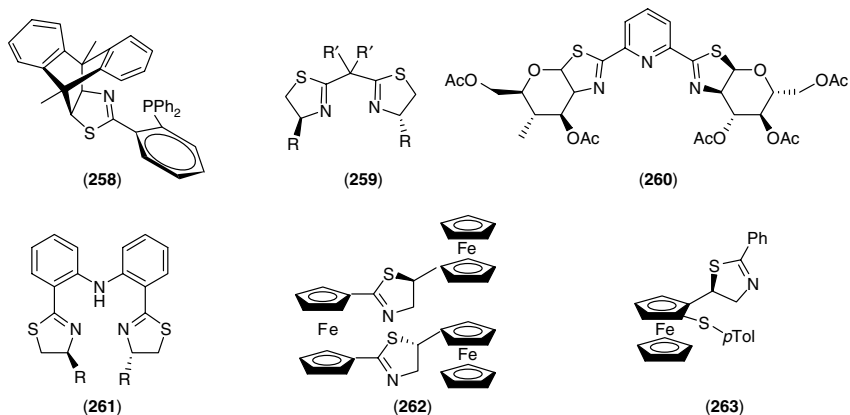


Scheme 6.136

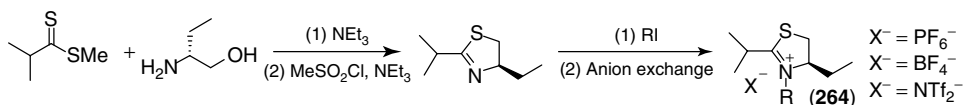
With the aim to study the oxidation of thiazolines into thiazolines dioxide, thiazolines 251–253 have been prepared from  $\beta$ -amino alcohols in two steps (Scheme 6.134); the cyclization occurred in the presence of the simple reagent phosphorus pentasulfide [239].

Park *et al.* described an enantioselective synthesis of alkylcysteines via phase-transfer catalytic alkylation of 2-aryl-2-thiazoline-4-carboxylate ester, by using the chiral catalyst 254. This methodology seems very efficient, given the mild reaction conditions and the high enantioselectivity obtained in the most cases (Scheme 6.135) [240].

In a very elegant synthesis of cyclic oligothiazolines, Fukuyama and coworkers [241] have built the thiazolidine ring from  $\beta$ -lactone 255 with thiobenzoic ester to provide in two steps the monothiazoline unit 256, which was submitted to repetitive elongation to give ultimately the cyclic oligothiazoline 257 (Scheme 6.136).



Scheme 6.137



Scheme 6.138

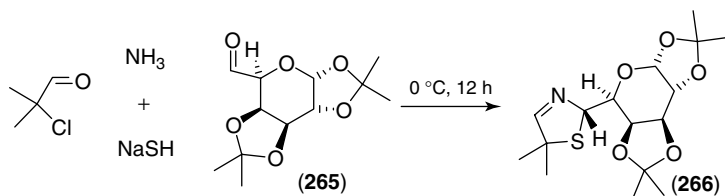
The first application of a chiral bis(thiazoline) ligand for an asymmetric hydrosilylation reaction was reported by Helmchen *et al.* [242]. Since then, a few promising examples have been reported for asymmetric catalytic reactions with thiazolines or bis-thiazolines as ligands, such as Diels–Alder reactions (with ligands **258** and **259**) [243], cyclopropanation (in the presence of the carbohydrate-derived pyridyl bis(thiazoline) **260**) [244] and allylic substitution (with ligands **259**) [245] (Scheme 6.137).

$C_2$ -symmetric tridentate bis(thiazoline) ligands **261** were used in catalytic asymmetric Henri reaction (nitroaldol reaction); an interesting metal-controlled reversal of enantioselectivity was obtained by replacing Cu(II) with Zn(II) [246]. In order to use them as ligands for asymmetric catalysis, new chiral ferrocene-thiazolines with (ligand **262**) [247] and without (ligand **263**) [248]  $C_2$  symmetry have been synthesized.

A novel class of chiral ionic liquids based on the thiazolium cation **264** was prepared from amino alcohols in a multigram scale, as shown in Scheme 6.138. Their properties (low melting point, water tolerance and stable under acidic or basic conditions) make them interesting potential candidates for new chiral solvents [249].

### 6.3.2.2 3-Thiazolines

Very few enantioselective syntheses of 3-thiazolines have been reported in the literature. The first synthesis of enantiopure 3-thiazolines via an Asinger reaction was described by Martens and coworkers [250]. The easily accessible galactose



Scheme 6.139

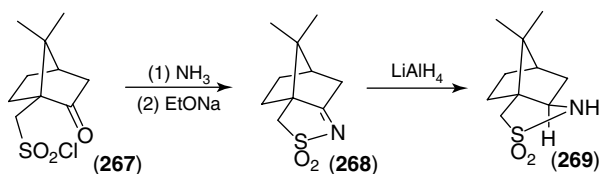
derivative **265** reacted under Asinger conditions to give 3-thiazolines **266** in good yields and in a highly diastereoselective way (Scheme 6.139).

### 6.3.3

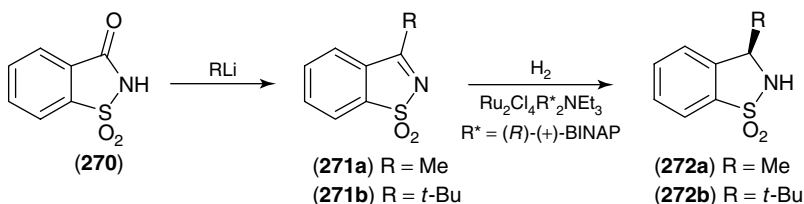
#### Sultams

Chiral  $\gamma$ -sultams are useful heterocycles for asymmetric synthesis and medicinal chemistry. The most important application concerned the use of these sultam derivatives as chiral auxiliaries. In 1984, Oppolzer described the synthesis of the camphor-derived sultam **269** (named Oppolzer's camphor sultam auxiliary), which was easily prepared from (+)-camphor-10-sulfonyl chloride **267**, as shown in Scheme 6.140 [251].

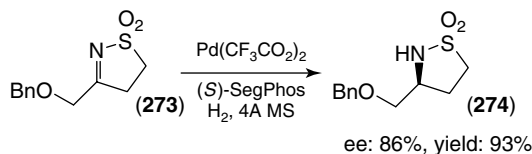
Many asymmetric syntheses of chiral sultams that are not derived from camphor have been developed [252]. Oppolzer and coworkers [253] have performed the synthesis of compounds **272a** and **272b**, which are structurally simpler than the compound **269** (Scheme 6.141). The product **272a** was obtained in two steps from saccharine **270**. The key step was the asymmetric hydrogenation of imine **271** catalyzed by  $\text{Ru}_2\text{Cl}_4[(R)-(+)\text{-BINAP}]_2(\text{NEt}_3)$ . While the reduction of **271a** furnished, after crystallization, the enantiomerically pure sultam **272a**, reaction from imine **271b** gave only traces of the racemic **272b**. An alternative approach consisted in the resolution of the racemic **272b**.



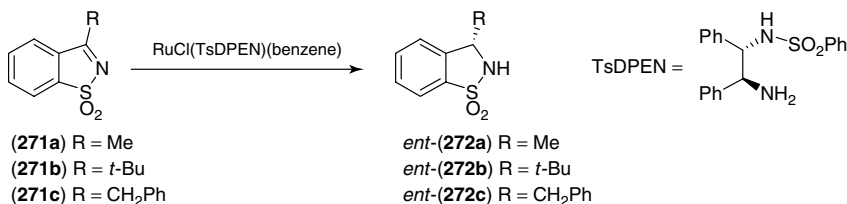
Scheme 6.140



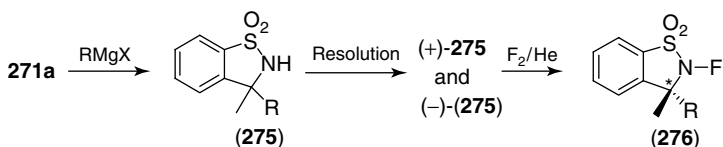
Scheme 6.141



Scheme 6.142



Scheme 6.143



Scheme 6.144

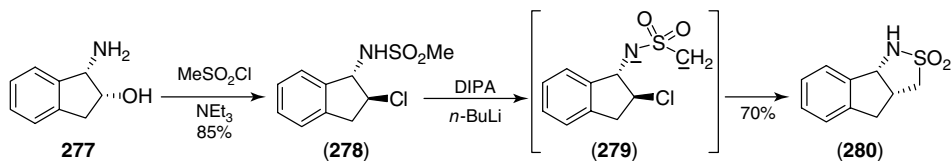
The Pd/phosphine complexes were found to be valuable catalysts for the asymmetric hydrogenation of a series of cyclic sulfonamides **271** [254]. For example, Scheme 6.142 shows the first enantioselective synthesis of the chiral sultam **274** from the sulfonamide **273**.

The asymmetric transfer hydrogenation of imines **271** catalyzed by ruthenium and rhodium complexes led to the corresponding sultams in good to excellent enantiomeric excesses (Scheme 6.143) [255]. Ahn *et al.* reported a practical synthesis of the sultams *ent*-**272a–c** by using Noyori's RuCl(*N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN))(benzene) catalyst as hydrogen donor. The sultam auxiliaries *ent*-**272** were obtained in high enantiomeric excess (93% > ee > 91%) [256].

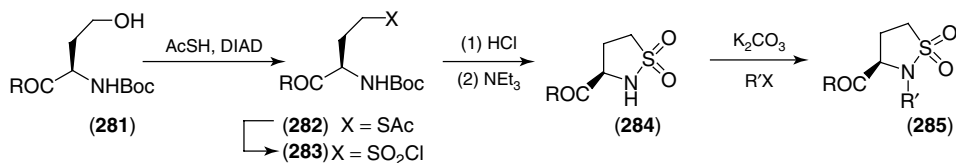
All these sultams have been shown to be highly selective chiral auxiliaries in asymmetric alkylations [257], aldol reactions [258], radical additions [259], Diels–Alder reactions [260], addition reactions [261], cyclopropanation [262], epoxidation [263], azidation [264], ene-reaction [265], asymmetric Bayliss – Hillman reaction [266], and so on.

With a view to synthesizing new chiral fluorinating agents, some authors reported the synthesis of chiral sultams with a stable but reactive N–F bond [267], such as compound **276** obtained by the fluorination of enantiopure compound **275** (Scheme 6.144).

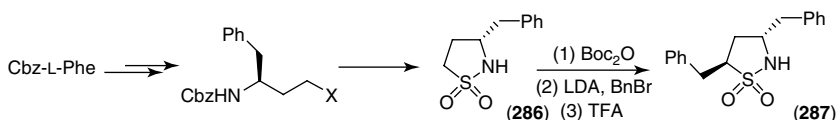
Chiral  $\beta$ -amino alcohols were used as precursors for the synthesis of chiral halosulfonamides and sultams [268]. In the case of the *cis*-aminoindanol **277**, the hydroxyl group was converted to the *trans*- $\beta$ -halosulfinamide **278** with inversion



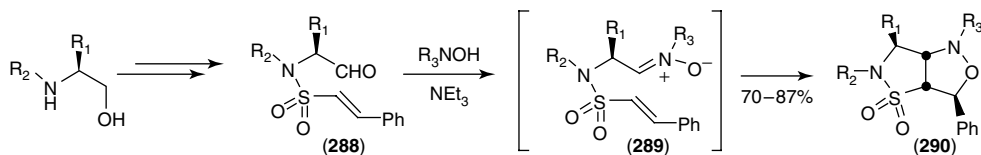
Scheme 6.145



Scheme 6.146



Scheme 6.147



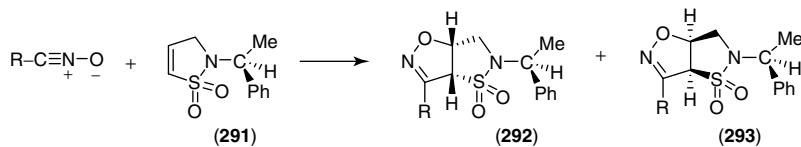
Scheme 6.148

of configuration. Sultam **180** was obtained via the intramolecular sulfonamide dianion **279** alkylation, as shown in Scheme 6.145.

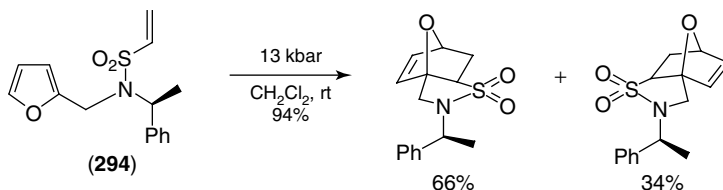
The synthesis of enantiopure sultam **285**, a potential anti-inflammatory agent [269, 270], was accomplished from chiral alcohols **281** that were converted to the thioacetate **282**. Chlorine oxidation followed by selective *N*-Boc removal and cyclization gave **284**, which is a precursor of the target compound **285** (Scheme 6.146).

A novel series of HIV protease inhibitors containing the sultam scaffold **287** has been synthesized from the enantiopure Cbz-L-phenylalanine [271]. Alkylation of sultam **286** led to the trans isomer **287** as the sole isomer (Scheme 6.147).

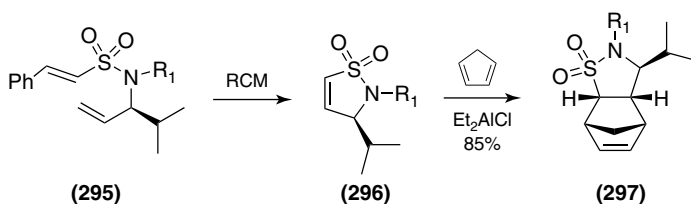
Bicyclic sultams **290**, including an isoxazoline or isoxazolidine moiety, have been synthesized by intramolecular cycloaddition of sulfonamide oxime **289** [272]. This occurs with a complete diastereoselectivity: the stereochemical information present in the dipolarophile was completely preserved in the cycloadducts and the stereochemistry was predetermined by the alkene geometry, as outlined in Scheme 6.148.



Scheme 6.149



Scheme 6.150



Scheme 6.151

Scheme 6.149 describes an intermolecular version of this 1,3-dipolar cycloaddition by using the chiral sultam **291** and nitrile oxide as starting materials. The reaction led to a separable 1:1 diastereoisomeric mixture of the bicyclic sultams **292** and **293** [273].

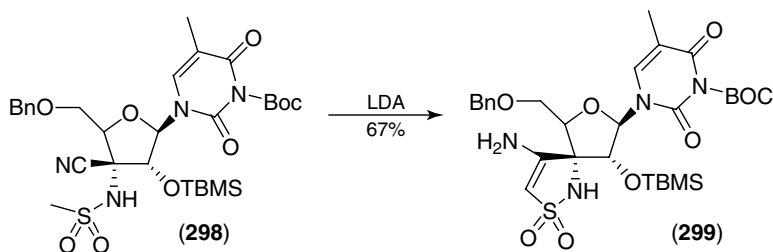
Enantiopure sultams have been readily prepared by intramolecular Diels-Alder reaction of the furan-containing vinylsulfonamides **294**, but with a relatively low diastereoselectivity, as shown in Scheme 6.150 [274].

$\alpha$ - $\beta$ -Unsaturated- $\gamma$ -sultams **296** were generated via ring-closing metathesis (RCM) [275]; these sultams reacted with cyclopentadiene under Lewis acid catalysis to yield the tricyclic sulfonamides **297** with complete facial and endo selectivity (Scheme 6.151).

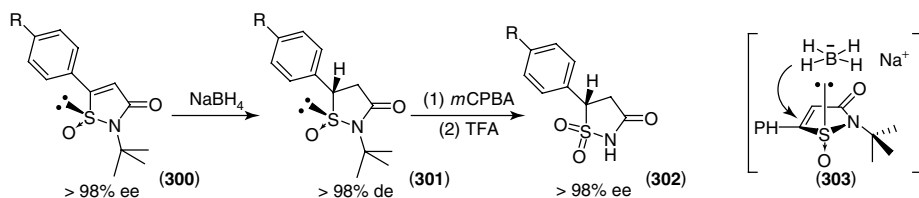
With the aim of synthesizing a new class of nucleoside analogs with a specific inhibition against the HIV-1, Postel and coworkers reported the synthesis and the treatment of new cyanomethanesulfonamides of monosaccharidic and nucleosidic substrates under carbanion-mediated sulphonamide intermolecular coupling (CSIC) conditions [276]. This reaction, depicted in Scheme 6.152, led to the dihydroisothiazole 1,1-dioxide **299** in good yields.

Recently, Combs and coworkers [277] described the first asymmetric synthesis of compound **302** from the enantiopure sulfoxide **300**. The key step of this synthesis was the reduction of the heterocycle with excellent regiochemical and stereochemical controls (Scheme 6.153). The hydride attacked the ethylenic double

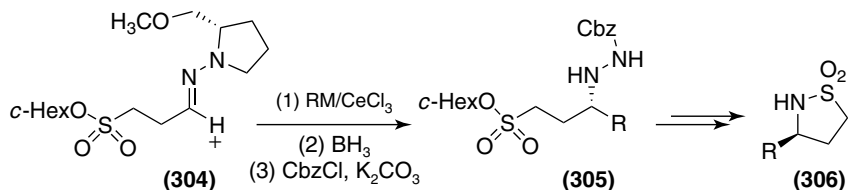




Scheme 6.152



Scheme 6.153



Scheme 6.154

bond adjacent to the sulfonamide on the opposite face of the heterocycle that bears the sulfonamide oxygen, as depicted on model **303**.

Enders and coworkers [278] have developed an efficient asymmetric synthesis of 3-substituted  $\gamma$ -lactams through the diastereoselective nucleophilic 1,2-addition of various organocerium compounds to the CN double bond of  $\omega$ -S-1-amino-2-methoxymethylpyrrolidine (SAMP)-hydrazonosulfonates **304**. Compounds **306** were obtained in good overall yields and with high enantiomeric excesses (Scheme 6.154).

As can be seen from the above discussion, five-membered heterocycles with N, O and S atoms constitute a large category of highly valuable reagents. Their value is clearly noticeable in the field of asymmetric synthesis as well as biologically active compounds. As a matter of fact, these compounds not only act as chiral auxiliaries (some of them even belonging to very classical stereoselective reactions) but also as chiral ligands linked to metal catalysts, which allow various remarkable enantioselective transformations in many diverse topics. Though revealed more recently as important pharmaceutical tools, their usefulness in this area cannot be underestimated and the ongoing extensive research should lead to still more promising results.

## References

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## 7

## Asymmetric Synthesis of Six-Membered Ring Nitrogen Heterocycles with More Than One Heteroatom

*Péter Mátyus and Pál Tápolcsányi*

## 7.1

### Six-Membered Rings with Another Heteroatom in the Same Ring

This chapter covers the synthesis of chiral partially or fully saturated substituted pyridazines, pyrimidines, piperazines, oxadiazines, and morpholines with defined configuration of the substituents. Methods considering the formation of the heterocyclic ring are discussed separately from the stereoselective transformations by the involvement of the already existing ring.

A literature search was performed using the SciFinder program by using both keyword search (combination of the name of the corresponding ring with the keyword “asymmetric synthesis”) and structure search. In the latter case, for the corresponding ring given as “product”, unlimited substitution was allowed, but ring tools were locked out. The hits were refined (i) by omitting patents, (ii) by selecting the stereoselective reactions, and (iii) by the keyword “asymmetric synthesis”. The literature is surveyed covering the period from 1957 till 2007.

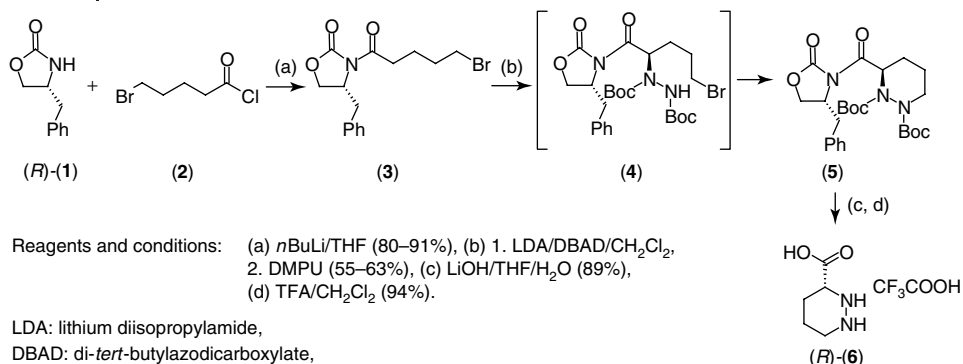
## 7.1.1

#### Pyridazines

Partially saturated pyridazine derivatives with defined chirality have so far been obtained via two different routes.

In the first, most frequently employed pathway, the key step is the ring closure of enantiomerically pure precursors to pyridazines. Such precursors have generally been (i) a lactone or lactam, (ii) a hydroxy ester or acid, (iii) an amino acid, (iv) a protected hydroxy aldehyde, (v) keto ester, or (vi) a chiral heterocycle.

The second route, which may be considered an important variant of the first, is based on the Diels–Alder reaction, which involves the cycloaddition of a chiral diene and azodicarboxylic ester or triazolo derivative as dienophile.



Scheme 7.1

### 7.1.1.1 Ring Closure of Optically Active Precursors

Piperazic acid (hexahydropyridazine-3-carboxylic acid) is a typical building block for a number of pharmacologically active compounds. Moreover, one of its enantiomers (3*S*) has been found to exert  $\gamma$ -aminobutyric acid (GABA) uptake inhibitory activity in rat cerebral cortex slices. Subsequently, enantioselective syntheses of such compounds have been thoroughly studied. Hale and coworkers described the synthesis of both enantiomers. The synthesis of (3*R*)-piperazic acid ((*R*)-6) starts with the N-acylation of (4*R*)-phenylmethyl-2-oxazolidinone (1) with 5-bromoaleryl chloride (2), followed by diastereoselective  $\alpha$ -hydrazination of 3 with di-*tert*-butylazodicarboxylate and  $\text{LiNiPr}_2$ . When the reaction was carried out in the presence of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone), the cyclized product 5 could be obtained directly without isolation of the intermediate bromovaleryl hydrazide 4. Interestingly, without the addition of DMPU, 4 was isolated as the major product. These findings were explained by the formation of a highly aggregated lithium-aza anion, which is transformed to a more reactive species in the presence of DMPU. After removal of the protecting groups from 5, (3*R*)-piperazic acid ((*R*)-6) was obtained as trifluoroacetate salt with 96% ee [1, 2]. The method has also been used for the preparation of (*S*)-piperazic acid [3, 4].

An analogous, convenient procedure was developed for the preparation of the *S*-enantiomer of 6 by Hale's group, starting from an oxazolidinone precursor derived from norephedrine. The product in this case was obtained with a lower enantiomeric excess (88–93%).

Three other pathways for the synthesis of enantiomerically pure pyridazinecarboxylic acid derivatives have been described by Schmidt's group, which are based on cyclocondensation with hydrazone formation or cyclization with alkylation of  $\alpha$ - or  $\delta$ -hydrazinocarboxylic acids.

In method I, as the key step, asymmetric hydrogenation of dehydro amino acid derivative 7 in the presence of a chiral rhodium catalyst ((*R,R*)-(Rh(1,5-COD)) ( $\text{DIPAMP}$ )<sup>+</sup> $\text{BF}_4^-$ ) afforded amino ester 8 with high enantioselectivity. By treatment with  $\text{NaNO}_2$  in acetic acid, 8 was transformed into hydrazine derivative 9, in which

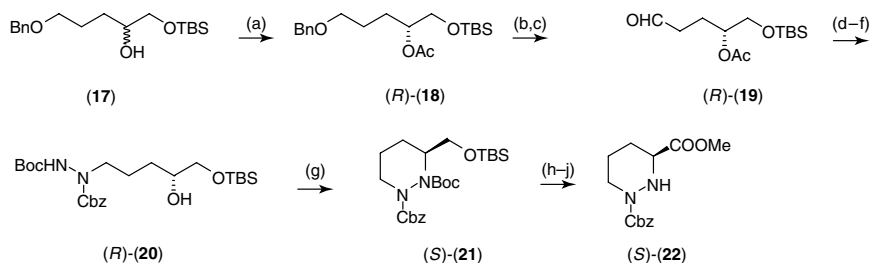




resolution of protected alcohol **17** gave the (*R*)-acetate (*R*)-**18** and the corresponding (*S*)-alcohol with high enantiomeric purity. The reaction conditions were thoroughly studied: application of *n*-hexane as solvent led to the best chemical yields and enantiomeric ratios, whereas basic additives such as pyridine, 4-*N,N*-dimethylaminopyridine, 2,4- and 2,6-lutidine were found to increase reaction rates considerably. Compound (*R*)-**18** was debenzylated and subsequently oxidized to aldehyde (*R*)-**19** with Dess–Martin reagent. Treatment of (*R*)-**19** with *tert*-butyl carbazate and NaBH<sub>3</sub>CN, and then protection with benzyloxycarbonyl group, led to compound (*R*)-**20**. For its cyclization to (*S*)-**21**, an intramolecular Mitsunobu reaction was carried out. (*S*)-**21** was transformed to piperazic acid derivative (*S*)-**22** with 98% ee [7].

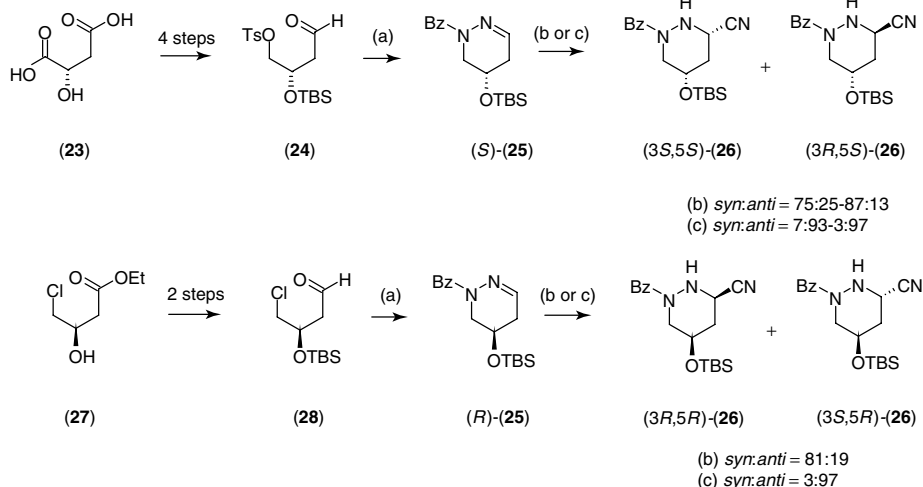
Four possible stereoisomers of 5-hydroxypiperazic acid were synthesized starting from chiral compounds **23** and **27**, which were transformed to the corresponding O-protected 3-butyraldehyde derivatives **24** and **28**, respectively, possessing a good leaving group at position 4. Ring closure with hydrazine hydrate and subsequent N-protection with benzoyl chloride gave tetrahydropyridazine derivatives (*S*)-**25** and (*R*)-**25**. Their diastereoselective Strecker reaction was investigated with trimethylsilyl cyanide in the presence of a Lewis acid. Interestingly, when Zn(OTf)<sub>2</sub> was used as Lewis acid, together with NaOAc/AcOH as additives, the *syn* cyano products (3*S*,5*S*)-**26** or (3*R*,5*R*)-**26** were formed in higher amounts. However, when Mg(OAc)<sub>2</sub> was used in combination with acetic acid, the *anti* isomers (3*R*,5*S*)-**26** or (3*S*,5*R*)-**26**, respectively, were obtained as the major product [8].

Another series of dihydropyridazines, the 6-aryl-5-methyl-4,5-dihydropyridazin-3(2*H*)-ones (*R*)-**33** could be obtained in four steps from the respective arene. Friedel–Crafts acylation of arenes **29** with (2*R*)-2-chloropropanoyl chloride to **30**, followed by their S<sub>N</sub>2 reactions with benzyl methyl malonate in the presence of NaH, afforded **31**. The reason for using benzyl methyl malonate instead of dimethyl malonate was to suppress possible epimerization in the subsequent step, in which removal of one of the ester groups was needed. Debenzylation of **31** and



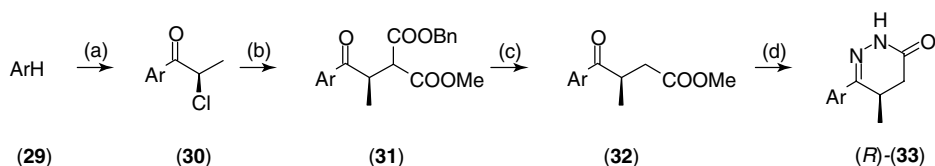
Reagents and conditions: (a) Lipase TL/CH<sub>2</sub>CHOAc/solvent/additive (11–62%, 82–98% ee), (b) H<sub>2</sub>/Pd–C/MeOH (quant), (c) Dess–Martin periodinane/CHCl<sub>3</sub> (99%), (d) 1. BocNHNH<sub>2</sub>/EtOH/AcOH, 2. NaCNBH<sub>4</sub> (67%), (e) CbzCl/NaHCO<sub>3</sub>/CHCl<sub>3</sub> (97%), (f) K<sub>2</sub>CO<sub>3</sub>/MeOH (73%), (g) DEAD/PPh<sub>3</sub>/THF (86%), (h) 1. TBAF/THF, 2. Jones reagent/acetone, (i) TMSCHN<sub>2</sub>/MeOH (81%), (j) TFA/CH<sub>2</sub>Cl<sub>2</sub> (84%).

Scheme 7.4



Reagents and conditions: (a) 1.  $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}/\text{EtOH}$ , 2.  $\text{BzCl}/\text{pyridine}$  (89–93%), (b)  $\text{Me}_3\text{SiCN}/\text{Zn}(\text{OTf})_2/\text{AcOH}/\text{NaOAc}/\text{CH}_2\text{Cl}_2$  (42–70%), (c)  $\text{Me}_3\text{SiCN}/\text{Mg}(\text{OAc})_2/\text{CH}_2\text{Cl}_2$  (75–99%).

Scheme 7.5



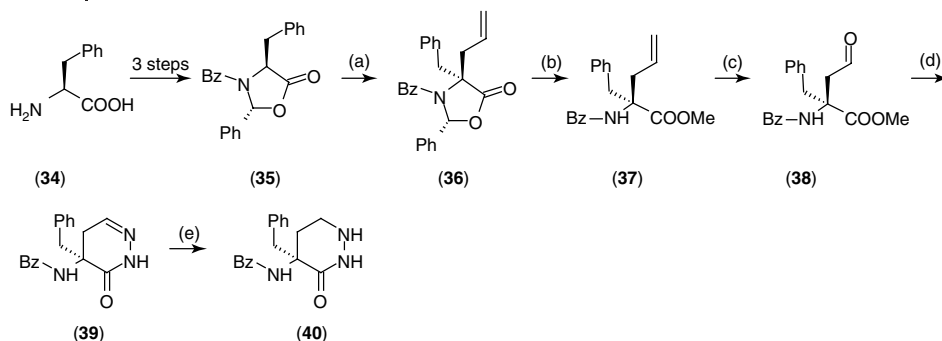
ArH: acetanilide, 2-isopropylpyrazolo[1,5-a]pyridine

Reagents and conditions: (a) (2R)-2-chloropropanoyl chloride/ $\text{AlCl}_3$ /1,2,4-trichlorobenzene (59–80%), (b)  $\text{NaH}/\text{CH}_2(\text{COOMe})(\text{COOBn})/\text{DMF}$  (81–84%), (c) 1.  $\text{Pd}-\text{C}/\text{H}_2/\text{EtOAc}$ , 2. diglyme/rfx (55–84%), (d)  $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}/\text{AcOH}/\text{MeOH}/\text{H}_2\text{O}$  (69–91%, 84–90.2% ee).

Scheme 7.6

subsequent decarboxylation gave monoesters **32**, which cyclized to pyridazinones (R)-**33** in 84–90.2% ee on treatment with hydrazine hydrate [9, 10].

Diastereoselective synthesis of tetrahydropyridazinone **40** as a precursor of  $\beta$ -strand mimetics has been described starting from (S)-phenylalanine (**34**), which was first transformed to phenyloxazolidinone **35**. Alkylation of **35** with allyl bromide in the presence of lithium hexamethyl-disilazide ( $\text{LiHMDS}$ ) selectively furnished allyl derivative **36** as the single isomer. Subsequent hydrolytic ring opening, followed by treatment with diazomethane, gave the  $\alpha, \alpha$ -dialkylated ester **37**. Ozonolysis of the double bond and the subsequent ring closure of aldehyde **38** led to dihydropyridazinone **39**, which could be hydrogenated to tetrahydroderivative **40** upon treatment with  $\text{NaBH}_3\text{CN}$  [11].

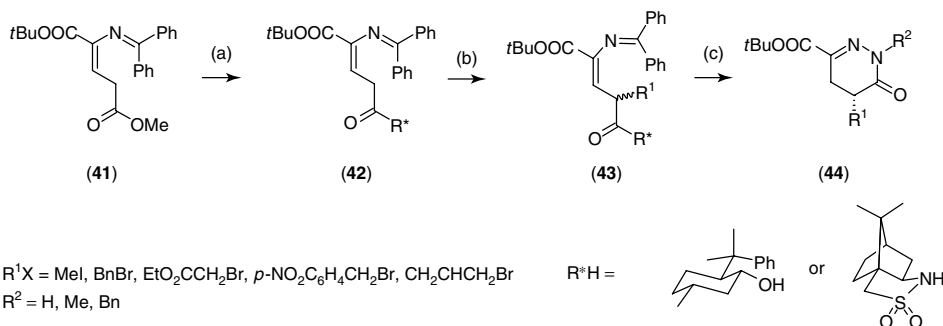


Reagents and conditions: (a) LiHMDS/allyl bromide/THF (93%, 95% ee), (b) 1. NaOH/MeOH, 2.  $\text{CH}_2\text{N}_2$  (99%), (c)  $\text{O}_3/\text{CH}_2\text{Cl}_2/\text{MeOH}$  (96%), (d)  $\text{N}_2\text{H}_4$  (85%), (e)  $\text{NaCNBH}_3/\text{MeOH}$  (73%).

**Scheme 7.7**

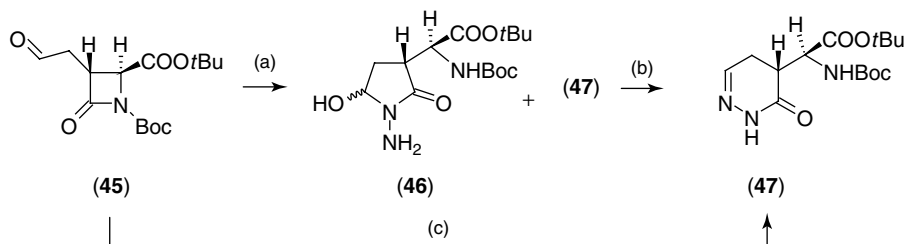
Asymmetric  $\gamma$ -alkylation of  $\alpha$ ,  $\beta$ -unsaturated glutamic acid derivatives **42** possessing a chiral auxiliary was the key step in the synthesis of 4-substituted 4,5-dihydropyridazinones **44**. Compounds **42** were obtained by selective  $\text{Me}_3\text{Al}$ -mediated acylation of methyl ester **41** with (2*R*)-bornane-10,2-sultam or 8-phenylmenthol. Alkylation of **42** was carried out under phase transfer-catalyzed conditions with various electrophiles, affording **43** with high diastereomeric excess (70–100% de) in favor of the 2*R* isomer. Reaction of the alkylated derivatives **43** with hydrazines afforded dihydropyridazinones **44** via N-deprotection and cyclization in one pot, with recovery of the chiral auxiliary [12].

Chiral pyridazine derivatives were synthesized by Young's group. They applied a "ring switching" method, starting from another optically active heterocyclic compound. Reaction of the  $\beta$ -lactam **45**, bearing a formylmethyl group, with hydrazine hydrate in methanol at room temperature gave a mixture of hydroxypyrrolidinones **46** (62%) and tetrahydropyridazine **47** (17%). Interestingly, reaction of the aldehyde



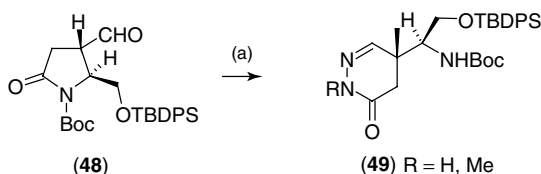
Reagents and conditions: (a)  $\text{Me}_3\text{Al}/\text{R}^*\text{H}$  (80%), (b)  $\text{R}^1\text{X}/\text{NaOH}/n\text{Bu}_4\text{NCl}/\text{MeCN}$  (30–90%, 70–100% de), (c)  $\text{R}^2\text{NHNH}_2/\text{EtOH}$  (90–95%).

**Scheme 7.8**



Reagents and conditions: (a)  $\text{NH}_2\text{NH}_2/\text{MeOH}/\text{rt}$  (**46**: 62%, **47**: 17%), (b) heating, (c)  $\text{NH}_2\text{NH}_2/\text{benzene}/\text{rt}$  (65%).

Scheme 7.9



Reagents and conditions: (a)  $\text{RNHNH}_2/\text{MeOH}/\text{rt}$  (41–65%).

Scheme 7.10

with hydrazine hydrate in refluxing benzene afforded **47** in 65% yield as the sole product [13].

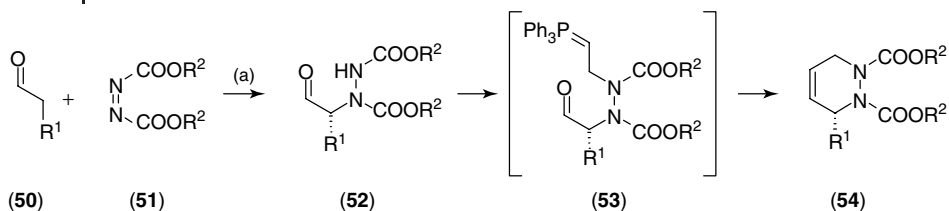
The ring switching method could also be successfully applied to functionalized pyrrolidinone derivative **48**, when dihydropyridazinones **49** were obtained in moderate to good yields [14].

An elegant one-pot method was recently described for the enantioselective synthesis of 3-substituted tetrahydropyridazines from achiral starting materials, using a chiral organocatalyst. In the first step, asymmetric catalytic  $\alpha$ -amination of aldehydes **50** with azodicarboxylates **51** in the presence of (*S*)-proline or 5-[(2*S*)-pyrrolidin-2-yl]-5*H*-tetrazole as catalyst gave intermediates **52**. Base-promoted addition of the secondary nitrogen in **52** to vinylphosphonium bromide led to the ylide intermediate **53**, which could be cyclized to the product **54** in 69–99% ee [15].

#### 7.1.1.2 Diels–Alder Reactions

In stereoselective hetero-Diels–Alder reactions, the stereochemical outcome of the reaction could be determined by chiral auxiliaries present either on the diene or on the dienophile, or as a further possibility, asymmetric catalysis could be employed.

The 2,3,4,6-tetra-*O*-acetyl- $\beta$ -D-glucopyranosyl unit displayed an *Re*-face reactivity in the cycloaddition reactions of dienes **55** with azodicarboxylates **51**, furnishing cycloadducts **56** with high stereoselectivity. On removal of the protective groups, **56** can be transformed to tetrahydropyridazine ester (*S*)-**57**. The benzyl ester of **56**

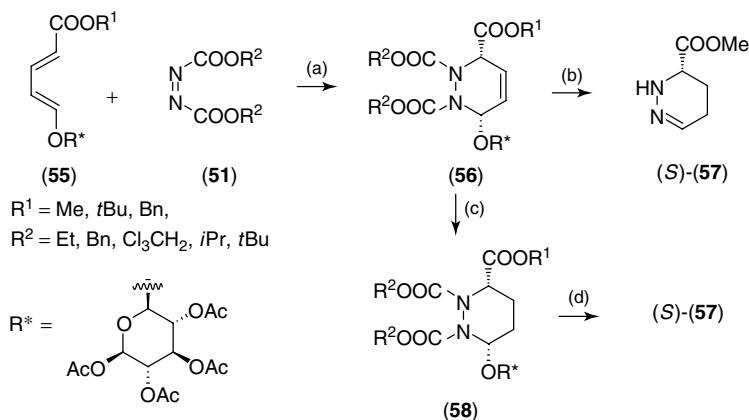


$R^1 = i\text{Pr}, t\text{Bu}, \text{allyl}, \text{Bn}$

$R^2 = \text{Et}, t\text{Bu}, \text{Bn}$

Reagents and conditions: (a) 1. Proline or 5-[(2*S*)-pyrrolidin-2-yl]-5*H*-tetrazole/ $\text{CH}_2\text{Cl}_2$ ,  
2.  $\text{CH}_2\text{CHPhPPh}_3\text{Br}/\text{NaH}/\text{DMSO}$  or THF (63–89%, 69–99% ee).

Scheme 7.11



Reagents and conditions: (a)  $\text{EtOAc}/70^\circ\text{C}$  or toluene/ $100^\circ\text{C}$  (57–87%),

(b)  $\text{H}_2/\text{Pd}-\text{C}/\text{EtOAc}$  ( $R^1 = \text{Me}$ ,  $R^2 = \text{Bn}$ ) (37%, 98% ee),

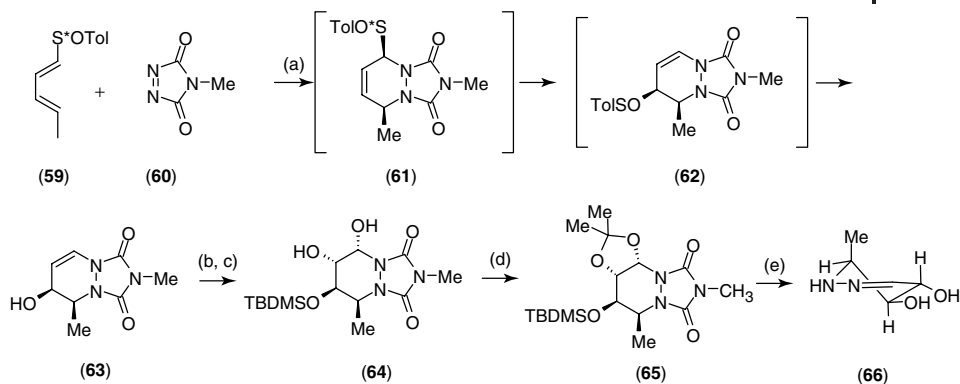
(c)  $\text{H}_2/\text{Pd}-\text{C}/\text{EtOAc}$  ( $R^2$  not Bn) (82–93%), (d) TFA ( $R^1 = \text{Me}$ ,  $R^2 = t\text{Bu}$ ) (57%).

Scheme 7.12

furnished (*S*)-57 directly, while hydrogenolysis of *tert*-butyl esters afforded saturated derivatives 58, which were then treated with trifluoro-acetic acid (TFA) to yield (*S*)-57 [16].

Oxazolidinethione moiety was applied as chiral auxiliary in an analogous Diels–Alder reactions of (4*R*)-3-[(1*E*)-buta-1,3-dien-1-yl]-4-phenyl-1,3-oxazolidine-2-thione with diethyl azodicarboxylate to furnish the product in moderate stereoselectivity (50% de) [17].

(3*S*,4*R*,5*R*)-4,5-Dihydroxy-3-methyl-2,3,4,5-tetrahydropyridazine 66 has been prepared from triazolocarbinal 63 derived from [(*S*)-*R*]-[(1*E*,3*E*)-1-*p*-tolylsulfinyl]-1,3-pentadiene (59) and 4-methyl-1,2,4-triazoline-3,5-dione (60) in an asymmetric tandem hetero-Diels–Alder cycloaddition [2, 3] – sigmatropic rearrangement – sulfenate trapping reaction. After protection of the hydroxy group of 63, the



Reagents and conditions: (a)  $\text{P(OMe)}_3$  (b)  $\text{TBDMSOTf/Et}_3\text{N}$  (57%), (c)  $\text{OsO}_4\text{-NMO/acetone-H}_2\text{O}$  (54%, 80% de), or (trifluoromethyl)methyldioxirane (64%, 98% de), (d)  $\text{DMP/TsOH/acetone}$  (75%), (e)  $\text{NH}_2\text{NH}_2$  (quant).

TBDMS: *tert*-butyldimethylsilyl

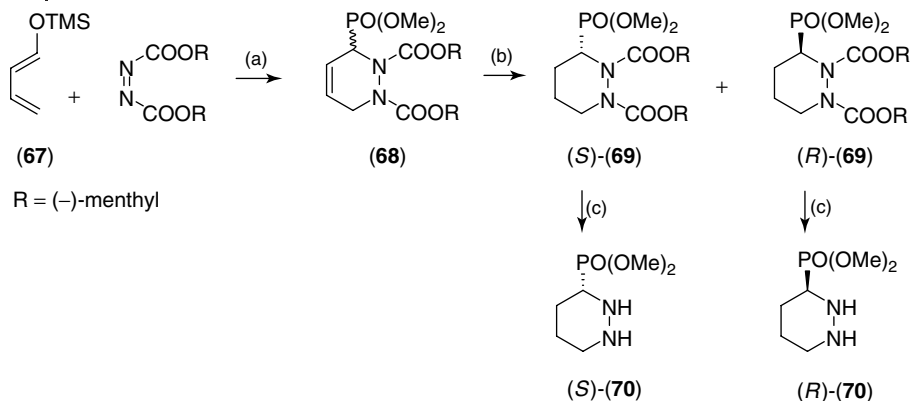
**Scheme 7.13**

*tert*-butyldimethylsilyl derivative was dihydroxylated in the presence of  $\text{OsO}_4$ , yielding **64** with 80% de and 54% yield. When (trifluoromethyl)methyldioxirane was the oxidizing agent, 98% de and 64% yield were attained. Transformation of *cis* diol **64** to acetonide **65** and subsequent hydrazinolysis resulted in pyridazine derivative **66** [18].

The cycloadduct from the analogous diastereoselective aza-hetero-Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with (4*S*)-4-benzyl-3-[(2*E*)-penta-2,4-dienyl]-1,3-oxazolidin-2-one in the presence of titanium tetrachloride (dr: 97:3) could be transformed to the trifluoroacetate of *S*-piperazic acid (*S*)-**6** via a series of steps [19].

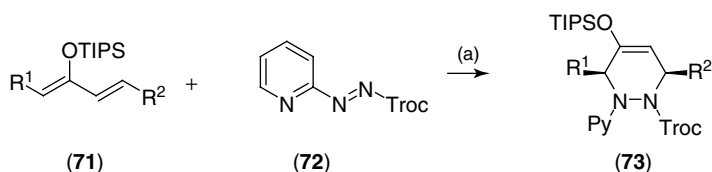
According to the other approach, a chiral auxiliary was built in the dienophile. Thus, the asymmetric synthesis of piperidazine-3-phosphonic acid enantiomers was performed via a one-pot process of hetero-Diels–Alder reaction and subsequent phosphorylation. The reaction of diene **67** with dimethyl azodicarboxylate in the presence of trimethyl phosphite and trimethylsilyl triflate as Lewis acid gave an isomeric mixture of 3-(dimethoxyphosphoryl)-3,6-dihydropyridazine-1,2-dicarboxylate **68**. After catalytic hydrogenation, the saturated derivatives could be separated by chromatography, affording (*S*)-**69** and (*R*)-**69** in the ratio of 66:34. Subsequent hydrolysis gave (*S*)-**70** and (*R*)-**70**, respectively [20].

The reactions of variously functionalized dienes **71** with azopyridine **72** have been investigated in the presence of chiral catalysts. A combination of (*R*)-2,2'-Bis(dimethylphosphino)-1,1'-binaphthalene (BINAP) and  $\text{AgOTf}$  as catalyst and propionitrile as solvent provided the most effective reaction conditions, affording products **73** in good yields and high enantiomeric purity for most substrates [21].



Reagents and conditions: (a)  $\text{P}(\text{OMe})_3/\text{TMSOTf}/\text{CH}_2\text{Cl}_2$ , (b)  $\text{H}_2/\text{Pd}-\text{C}/\text{MeOH}$  (99%, 66:34 dr), (c) 1. 6 N  $\text{HCl}/\text{AcOH}$ , 2. propylene oxide (64–67%).

Scheme 7.14



$\text{R}^1 = \text{Me}, \text{Bn}, 4\text{-MOMO-Bn}, (\text{CH}_2)_3\text{OTBS}$

$\text{R}^2 = \text{Me}, \text{Ph}, i\text{Bu}, i\text{Pr}, \text{BOM}, 2\text{-furyl}$

Reagents and conditions: (a) 5 mol% (R)-BINAP/10 mol%  $\text{AgOTf}/\text{EtCN}$  (65–87%, 55–99% ee).

Scheme 7.15

### 7.1.2

#### Pyrimidines

For the synthesis of substituted pyrimidines with defined stereochemistry, condensation of an enantiomerically pure  $\beta$ -amino acid amide derivative with an aldehyde followed by the intramolecular addition of the amino nitrogen to the imine bond formed, in one pot or via separate steps, is a frequently applied method. The other most frequently used approach involves an intramolecular nucleophilic substitution as the ring closure step. Besides, stereoselective transformation such as alkylation, halogenation, or hydroxylation of the pyrimidine ring could also be employed.

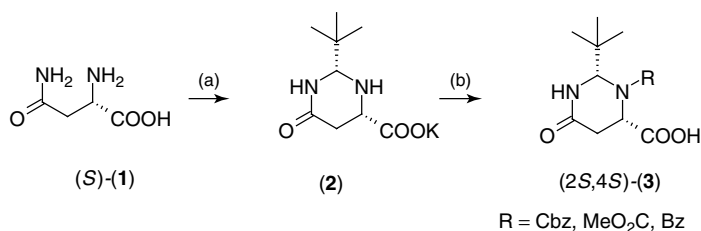
##### 7.1.2.1 Formation of the Pyrimidine Ring

**Ring Formation by Addition to Imine Bond [5 + 1] Types** Synthesis of (2*R*, 4*S*)-2-*tert*-butyl-6-oxohexahydropyrimidine-4-carboxylic acid and its protected derivatives (2*R*,4*S*)-3 has been reported in several papers. Thus, treatment of

(*S*)-asparagine (**1**) with pivaldehyde in the presence of KOH resulted in pyrimidinone **2** with *cis* orientation of the substituents as the single isomer. Protection of the amine nitrogen in **2** with benzyl chloroformate gave compound **3** [22–28].

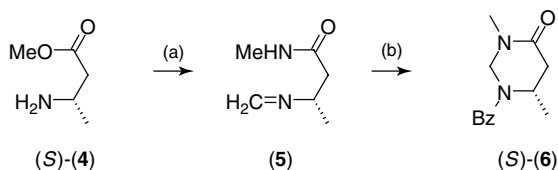
In an analogous way, (6*S*)-1-benzoyl-3,6-dimethyltetrahydropyrimidin-4(1*H*)-one ((*S*)-**6**) was prepared from methyl (*S*)-3-aminobutanoate (**4**) by conversion to amide with methylamine and subsequent Schiff's base formation to **5** followed by ring closure and subsequent benzylation [29].

The same method was applied for the synthesis of the phenyl derivative (*S*)-**10** by amide formation of methyl (*S*)-3-amino-3-phenylpropionate (**9**) with methylamine, followed by cyclization with formaldehyde. Compound (*S*)-**9** was prepared via diastereoselective addition of lithium (*R*)-benzyl( $\alpha$ -methylbenzyl)amide to *tert*-butyl cinnamate (**7**), followed by hydrogenolysis of **8** and subsequent esterification [30].



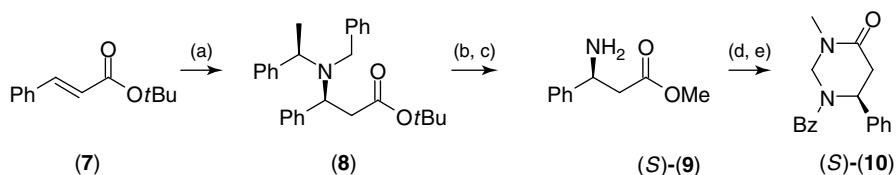
Reagents and conditions: (a) KOH/*t*BuCHO, (b) RCl/NaHCO<sub>3</sub>/H<sub>2</sub>O (67–80% from **1**).

Scheme 7.16



Reagents and conditions: (a) 1. MeNH<sub>2</sub>/MeOH, 2. (CH<sub>2</sub>O)<sub>*n*</sub> (79%),  
(b) BzCl/DMAP/benzene (92%).

Scheme 7.17



Reagents and conditions: (a) Li (*R*)-benzyl( $\alpha$ -methylbenzyl)amide, (b) H<sub>2</sub>/Pd-C/AcOH,  
(c) Me<sub>3</sub>SiCl/MeOH (69% from **7**), (d) 1. MeNH<sub>2</sub>/MeOH,  
2. (CH<sub>2</sub>O)<sub>*n*</sub>, (e) BzCl/DMAP/benzene (82% from **9**).

Scheme 7.18

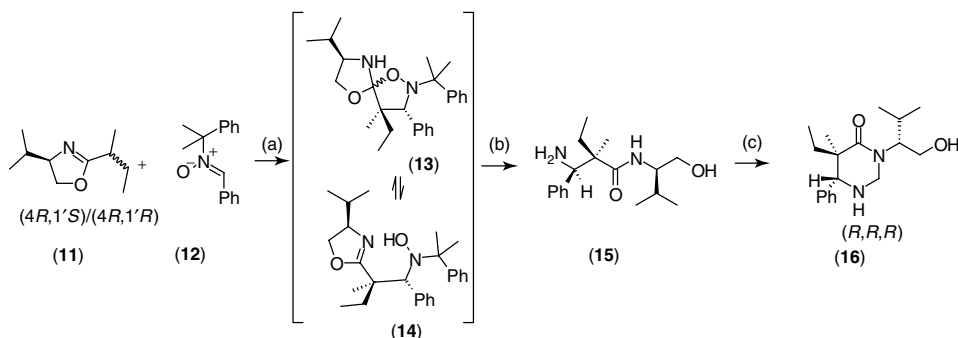


Optically active oxazoline **11** derived from D-valinol could be stereoselectively transformed to  $\beta$ -aminoalkanamide **15** and its substituted derivatives by addition of the lithium salt of **11** to *N*-cumyl nitron **12**. The addition afforded a mixture of the equilibrating spirocycle **13** and hydroxylamine **14**. Hydrogenation of the mixture gave **15** in a highly enantioselective way (dr: 93:7), which was subsequently converted to tetrahydropyrimidinone **16** by treatment with paraformaldehyde [31].

**Ring Closure by Intramolecular Nucleophilic Displacement** 1,3,6-Trisubstituted 2,4-dioxohexahydropyrimidines (*S*)-**21** could be synthesized via intramolecular nucleophilic attack of the terminal amino group to methyl ester in anilincarbonylamino diester intermediate (*S*)-**20**, which was prepared from partially protected aspartic acid (*S*)-**17**. Its activation with isobutyl chloroformate in the presence of *N*-methylmorpholine and the subsequent reaction of the mixed anhydride with diazomethane gave diazo compound (*S*)-**18**, which underwent the Arndt–Eistert rearrangement upon treatment with silver benzoate with methanol, leading to the homoaspartic acid derivative (*S*)-**19**. Hydrogenolysis, followed by addition to phenyl isocyanate, afforded the linear urea intermediate (*S*)-**20**, which, under basic conditions, cyclized regioselectively through the methyl ester and subsequently alkylated on the nitrogen, providing the 2,4-dioxohexahydropyrimidine derivative (*S*)-**21** [32].

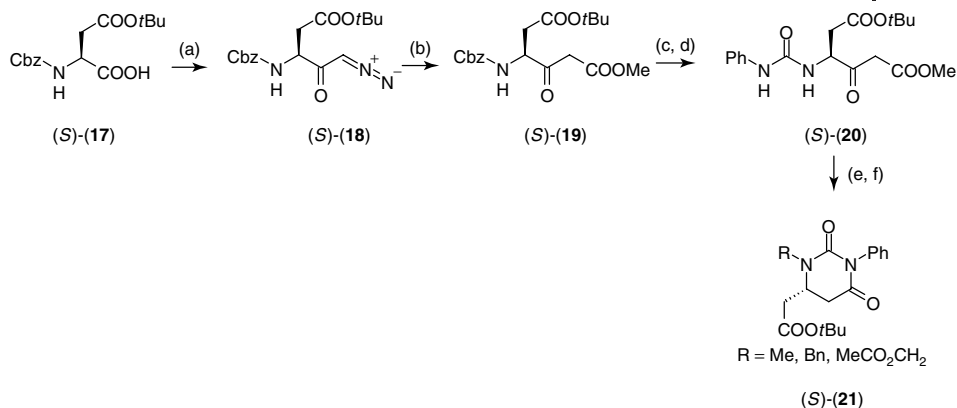
(*S*)-1-*tert*-Butyl-4-methyl 2-aminobutanedioate ((*S*)-**22**) was reacted with diphenyl cyanocarbonimidate (**23**) to give (*S*)-**24**, which was then treated with benzylamine, affording a 1:1 mixture of pyrimidine (*S*)-**25** and imidazole **26**. The latter showed little optical activity, but (*S*)-**25** was obtained with 80% ee. The same reaction sequence starting from (*R*)-1-*tert*-butyl-4-methyl 2-aminobutanedioate gave the enantiomeric (*R*)-**25** with 90% ee [33].

Dihydropyrimidinone derivative (*S*)-**30**, a precursor of the antibiotics TAN-1057A, has been synthesized from *N*-protected diamino acid (*S*)-**27**, which was coupled with *S*-methylisothiobiuret (**28**). Removal of the Boc-protecting group from (*S*)-**29**, followed by ring closure and subsequent hydrogenolysis, gave (*S*)-**30** in 87% ee [34].



Reagents and conditions: (a) *s*BuLi/THF, (b) H<sub>2</sub>/Pd–C/MeOH (98%, 93:7 dr), (c) (CH<sub>2</sub>O)<sub>n</sub>/MeOH (60%).

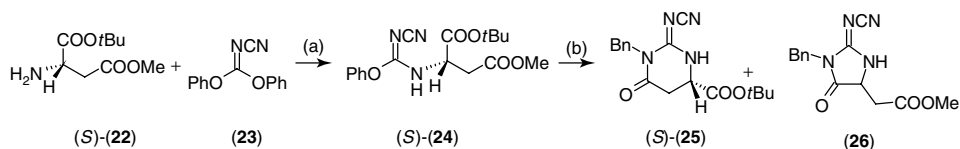
Scheme 7.19



Reagents and conditions: (a)  $i\text{BuOCOCli}/\text{NNM}/(\text{THF})/\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$ , (b)  $\text{PhCOOAg}/\text{Et}_3\text{N}/\text{MeOH}$ , (c)  $\text{H}_2/\text{Pd}-\text{C}/\text{MeOH}$ , (d)  $\text{PhNCO}/\text{THF}$ , (e)  $\text{KOtBu}/\text{THF}$  (70%), (f)  $\text{RX}/\text{KOtBu}/\text{THF}$  (80–93%).

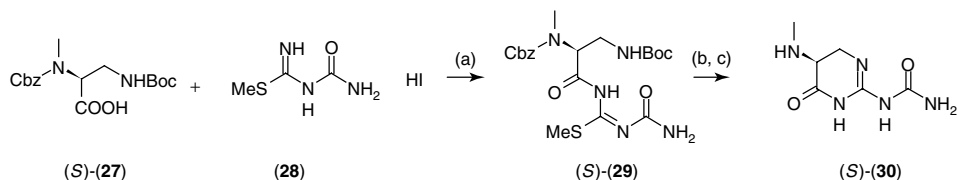
NNM: *N*-methylmorpholine

**Scheme 7.20**



Reagents and conditions: (a)  $i\text{PrOH}$  (84%, 100% ee), (b)  $\text{BnNH}_2/i\text{PrOH}$  (68% 1:1 mixture of  $(S)\text{-}25$  and  $26$ , 80% ee for  $(S)\text{-}25$ ).

**Scheme 7.21**



Reagents and conditions: (a)  $\text{HOBt}$ ,  $\text{EDC}$ ,  $\text{DIEA}$  (100%), (b) 1.  $\text{TFA}/\text{anisole}/\text{CH}_2\text{Cl}_2$ , 2.  $\text{Et}_3\text{N}/\text{AcOH}$  (55%, 92% ee), (c)  $\text{H}_2/\text{Pd}-\text{C}/\text{DMA}$  (96%, 87% ee).

$\text{HOBt}$ : 1-hydroxybenzotriazole

$\text{EDC}$ : 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride

$\text{DIEA}$ : *N,N*-diisopropylethylamine

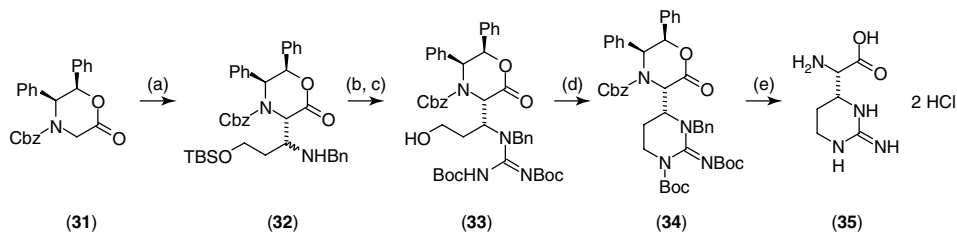
**Scheme 7.22**

For the asymmetric synthesis of  $(2S,3R)$ -capreomycinidine (**35**) as a structural unit of pentapeptides possessing tuberculostatic properties, the pyrimidine ring was elaborated by intramolecular Mitsunobu reaction. The synthesis started with the

preparation of the aluminum enolate of chiral morpholinone **31** by treatment with LiHMDS and subsequent transmetalation with  $\text{MeAl}_2\text{Cl}$ . Addition of O-protected *N*-benzyl-3-hydroxypropylidene amine to the aluminum enolate gave a mixture of two diastereomers **32**, in which the imine is situated on the opposite face of the morpholine ring rather than the phenyls. Guanidinylation of **32** with *N,N'*-di-*tert*-butoxycarbonyl-*S*-methylisothiurea in the presence of  $\text{HgCl}_2$  afforded a single diastereomer, which was deprotected to **33**. Formation of the pyrimidine ring was achieved by Mitsunobu reaction. Hydrogenolysis of the cyclized product **34** and subsequent acidic hydrolysis resulted in (2*S*,3*R*)-capreomycinidine (**35**) in over 99% ee [35].

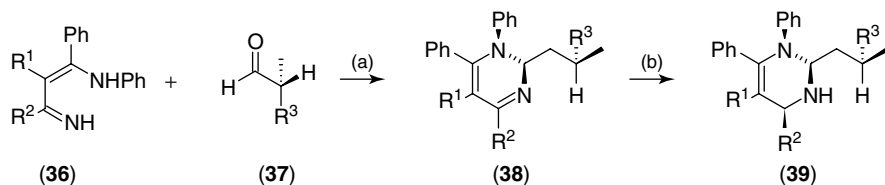
**Further Ring Closure Methods** 1,2-Dihydropyrimidines **38** were synthesized by the reaction of 3-aminoalkyl-2-enamines **36** with chiral aldehydes **37** in the presence of zinc chloride. Subsequent stereoselective reduction of **38** gave tetrahydroderivatives **39** in 99% de [36, 37].

Three-component Biginelli reactions between glycosylated aldehydes **40**, keto esters **41**, and urea (**42**) have been carried out in the presence of a mixture of  $\text{CuCl}$ , acetic acid and  $\text{BF}_3 \cdot \text{OEt}_2$  as additives for the synthesis of mono- and bis-*C*-glycosylated chiral dihydropyrimidinones **43** (due to asymmetric induction of the sugar moiety) with moderate to good (35–80%) stereoselectivities [38].



Reagents and conditions: (a) 1. LiHMDS, 2.  $\text{Me}_2\text{AlCl}$ , 3.  $\text{TBSOCH}_2\text{CH}_2\text{CH}=\text{NBn}$  (60%, 3.3:1 dr), (b) *N,N'*-di-*tert*-butoxycarbonyl-*S*-methylisothiurea/ $\text{HgCl}_2/\text{Et}_3\text{N}/\text{DMF}$  (67%), (c)  $\text{HF}/\text{MeCN}$  (81–91%), (d)  $\text{DIAD}/\text{PPh}_3/\text{THF}$  (87%), (e) 1.  $\text{H}_2/\text{PdCl}_2$ , 2.  $\text{HCl}$  (95%).

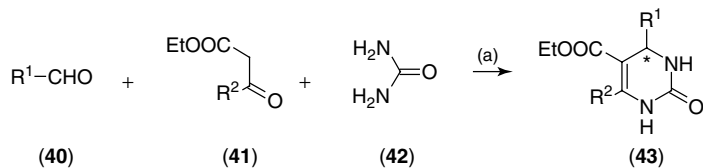
Scheme 7.23



$\text{R}^1 = \text{Me}, \text{Bn}, \text{CH}_2\text{CHCH}_2$   
 $\text{R}^2 = \text{Me}, \text{Ph}, p\text{-Tol}$   
 $\text{R}^3 = \text{Ph}, \text{BnO}$

Reagents and conditions: (a)  $\text{ZnCl}_2/\text{THF}$  (91%, 88–97% de), (b)  $\text{NaBH}_4/\text{MeOH}$  (quant, 99% de).

Scheme 7.24



$\text{R}^1$  = ribosyl, galactosyl, mannosyl, Ph, 2-( $\text{CF}_3$ )- $\text{C}_6\text{H}_4$

$\text{R}^2$  = Me, ribosyl, galactosyl, mannosyl

Reagents and conditions: (a)  $\text{CuCl}/\text{AcOH}/\text{BF}_3\cdot\text{Et}_2\text{O}$  (35–92%, 35–80% de).

**Scheme 7.25**

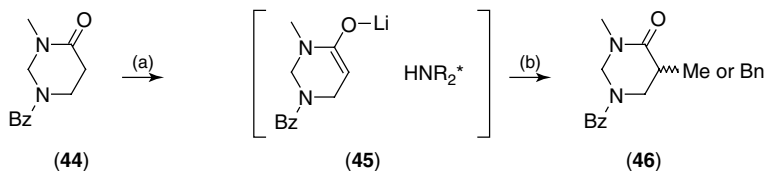
(*R*)-*N*-Boc-2,2-dimethyloxazolidine-4-carbaldehyde was subjected to the Biginelli reaction with ethyl acetoacetate and urea, with  $\text{Yb}(\text{OTf})_3$  as Lewis acid, furnishing the corresponding pyrimidinones as a 5:1 mixture of 4*R*,4'*S* and 4*S*,4'*S* diastereomers [39].

Asymmetric Biginelli reactions could also be performed starting from achiral components (benzaldehyde, ethyl acetoacetate, and urea) in the presence of  $\text{CeCl}_3$  or  $\text{InCl}_3$  as Lewis acid, using chiral diamine or amide ligands as additives. In this way, 4-phenyldihydropyrimidinone derivative **43** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{Me}$ ) could be obtained with moderate enantioselectivity (8–40%) [40].

#### 7.1.2.2 Stereoselective Transformation by the Involvement of the Pyrimidine Ring

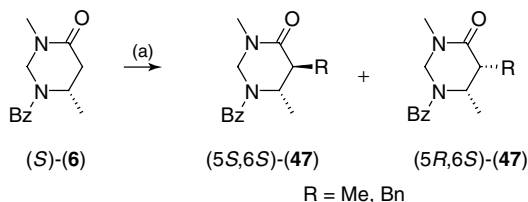
**Stereoselective Alkylations** In the presence of chiral amines, achiral pyrimidinone **44** was enantioselectively alkylated at 5-position in good yields with moderate (47:53–70:30) enantiomeric ratio. Lithium amides of the chiral amines were prepared with *n*BuLi, and the pyrimidinone **44** was treated with the chiral base obtained in this way, affording the lithium enolate of the heterocycle (**45**), which was then reacted with the corresponding electrophile. The enantioselectivity of the alkylation was the highest when (–)-sparteine was used as chiral amine, in toluene or tetrahydrofuran (THF) as solvent, and could be increased by the addition of LiBr. Moreover, a racemic mixture of alkylated pyrimidinones **46** could be enantiomerically enriched by deprotonation with lithium diisopropylamide (LDA), and subsequently reprotonated with a chiral proton source, achieving 53–68% ee [41].

A substituent with definite stereochemistry can determine the position of the entering electrophile in the C-alkylation of chiral substituted pyrimidinones. Compounds (*S*)-**6** could be stereoselectively alkylated at position 5 by deprotonation with



Reagents and conditions: (a)  $\text{LiNR}_2^*/\text{toluene}$ , (b) MeI or BnBr (70–92%, er (*S*:*R*) = 47:53 to 70:30).

**Scheme 7.26**



Reagents and conditions: (a) LDA/THF/Mel or BnBr/−75 °C (71–91%, dr *trans*:*cis* = 4:1).

**Scheme 7.27**

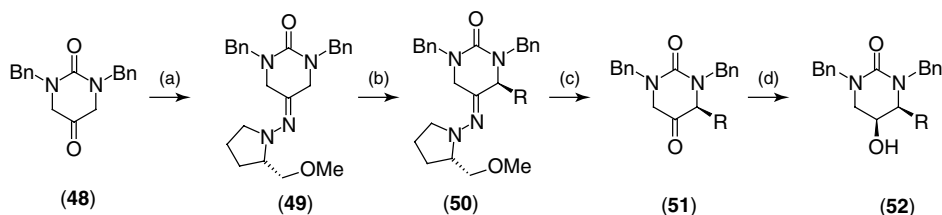
LDA and subsequent treatment with alkyl halides, furnishing a 4:1 mixture of the *trans* and *cis* diastereomers **47** [29].

Alkylation of (2*S*)-1-benzoyl-2-isopropyl-3-methyltetrahydropyrimidin-4(1*H*)-one was carried out in an analogous way, affording the products with the same stereoselectivity [27].

Considerably higher stereoselectivity (de > 95%) could be achieved in the C-alkylation of 5-alkyl-1-benzoyl-2(*S*)-*tert*-butyl-3-methylpyrimidinone at position 5 with various alkyl halogenides. Again, addition of the electrophile to the corresponding enolate preferably took place from the face opposite the *tert*-butyl group, leading to the 5-dialkylated product with the entering group *trans* to the *tert*-butyl group [42].

Asymmetric alkylation of the pyrimidine ring of **48** could be achieved under SAMP ((2*S*)-1-amino-2-(methoxymethyl)pyrrolidine) control as a temporary chiral auxiliary providing **50** via SAMP-hydrazone intermediates **49**. The hydrazone moiety was cleaved off, and the alkylated ketones **51** were then reduced to the corresponding 5-hydroxypyrimidin-2-ones **52** as potential HIV protease inhibitors [43].

Asymmetric induction via 1,5-radical translocation is used for the highly diastereoselective transformation of racemic and enantiomerically pure *N*-(*o*-bromo- and iodobenzoyl)-2-*tert*-butylperhydropyrimidinones **53** with electron-deficient alkenes

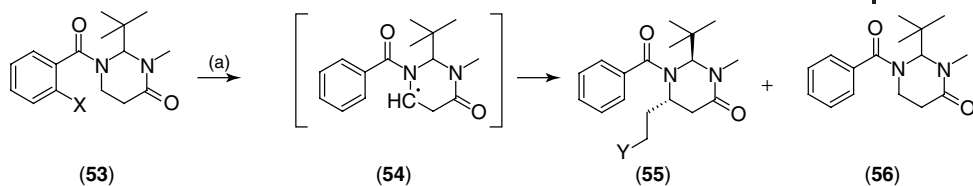


R = Me, Bu, CH<sub>2</sub>CHCH<sub>2</sub>, Bn, BnCH<sub>2</sub>

Reagents and conditions: (a) SAMP/CH<sub>2</sub>Cl<sub>2</sub>/MS (3A) (93%), (b) 2,2,6,6-tetramethylpiperidine/*n*BuLi/THF/RX, (c) dimethyldioxirane/acetone/MeCN/H<sub>2</sub>O or CuCl<sub>2</sub>/THF/H<sub>2</sub>O (44–59%, 2 steps), (d) LiAlH<sub>4</sub>/Et<sub>2</sub>O (76–84%, 96% de, 76–96% ee).

SAMP: (2*S*)-1-amino-2-(methoxymethyl)pyrrolidine.

**Scheme 7.28**



X = Br, I

Y = COOMe, CN, SO<sub>2</sub>Ph

Reagents and conditions: (a) *n*Bu<sub>3</sub>SnCl/NaCNBH<sub>3</sub>/AIBN/CH<sub>2</sub>=CH-Y/*i*BuOH  
(27–64% for 55, 16–70% for 56, over 95:5 dr).

AIBN: azobisisobutyronitrile.

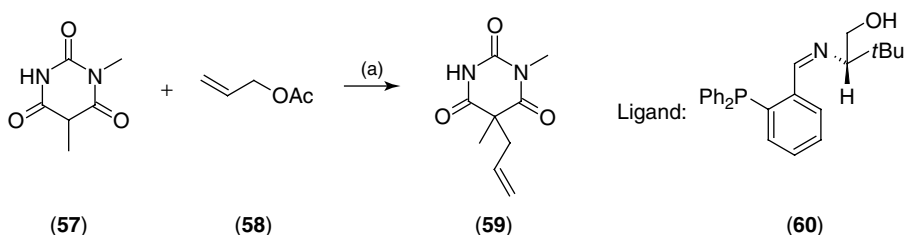
**Scheme 7.29**

to substituted derivatives **55**. Thus, reaction of racemic bromo- or iodoperhydropyrimidinone **53** with methyl acrylate, acrylonitrile or phenyl vinyl sulfone in the presence of a catalytic amount of *n*Bu<sub>3</sub>SnCl, NaCNBH<sub>4</sub>, and AIBN (azobisisobutyronitrile) resulted in a mixture of addition product **55** and reduced derivative **56**, in moderate yields and high stereoselectivity. With bromo derivatives as starting material, the expected product **55** is obtained as the major product, whereas reduced derivative **56** is formed in higher amount from the iodo compound. From enantiomerically pure **53**, products **55** are obtained in similar yields and high enantiomeric excess [44].

The palladium-catalyzed asymmetric allylic alkylation of barbituric acid derivatives with chiral ligands has been described. The reaction of 1,5-dimethylbarbituric acid (**57**) with allyl acetate (**58**) resulted in the 5-allyl substituted product **59** in moderate enantiomeric excess in the presence of Pd(acac)<sub>2</sub> as catalyst and **60** as phosphine ligand [45].

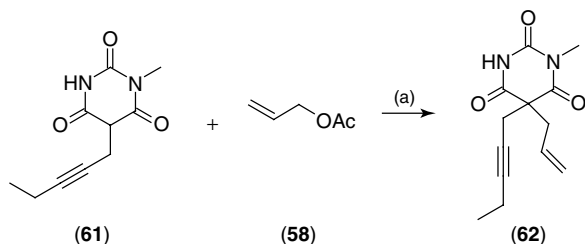
Low enantioselectivities (0–37% ee) were achieved in the reaction of barbiturate **61** with allyl acetate (**58**) in the presence of chiral phosphine ligands **65** or **66**. Using cyclopentenyl carbonate as the allylating agent, the product **64** was obtained in higher yields and enantioselectivities; however, the diastereomeric ratio was low [45].

Asymmetric allylic alkylation was also used for preparation of stereoisomeric mixtures enriched with one of the isomers of the narcotic methohexital, when



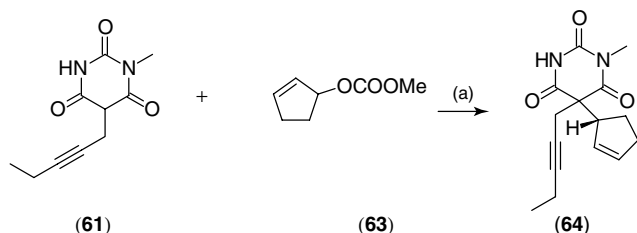
Reagents and conditions: (a) Pd(acac)<sub>2</sub>/DBU/toluene/CH<sub>2</sub>Cl<sub>2</sub>/ligand (77%, 34% ee).

**Scheme 7.30**

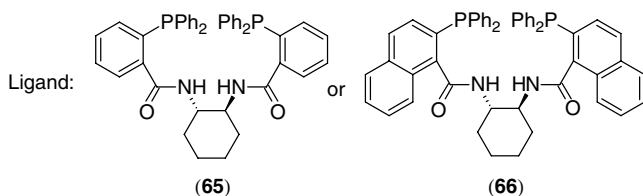


Reagents and conditions: (a)  $\eta^3\text{C}_3\text{H}_5\text{PdCl}_2$ ./ $\text{CH}_2\text{Cl}_2$  or DMSO/ligand (42–72%, 0–37% ee).

Scheme 7.31



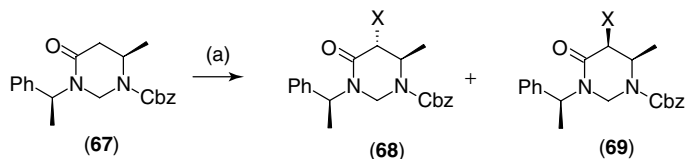
Reagents and conditions: (a)  $\text{Pd}_2\text{dba}_3 \cdot \text{CHCl}_3$ ./ $\text{CH}_2\text{Cl}_2$  or DMSO/ligand/54–93%, dr :1.1:1 to 2.51, 43–90% ee.



Scheme 7.32

reactions of 5-allyl-5-(2'-hex-3'-ynyl)-1-methylbarbituric acid with allyl acetate were performed under various conditions. Ratio of the isomers mainly depended on the phosphine ligands used [46].

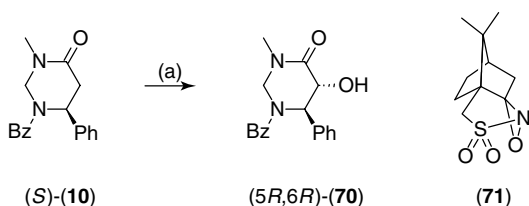
**Halogenation, Hydroxylation** Perhydropyrimidinone **67** could be halogenated via its enolate, formed by treatment with LiHMDS, using tosyl chloride, benzene-sulfonyl bromide, or iodine as the halogenating agent. The chlorination reaction proved to be more selective than the bromination. Shorter reaction times (15 min) generally, favored the formation of the *cis* products **69**, while after longer reaction times (hours) a reversal of the stereoselectivity was observed for both chlorination and bromination. The *cis* adducts **69** are the kinetically preferred products, and the *trans* derivatives **68** are the thermodynamically preferred compounds. In contrast, iodination led to the *trans* isomer as the major product even after a short reaction time [47].



X = Cl, Br, I

Reagents and conditions: (a) LiHMDS/THF/TsCl or PhSO<sub>2</sub>Br or I<sub>2</sub> (74–98%, dr = 10:90 to 85:15).

Scheme 7.33



Reagents and conditions: (a) 1. LDA, 2. oxaziridine **71**.

Scheme 7.34

Enolization of pyrimidinone (*S*)-**10** with LDA followed by hydroxylation with oxaziridine **71** resulted in the exclusive formation of hydroxy compound (*5R,6R*)-**72** [30].

### 7.1.3

#### Piperazines

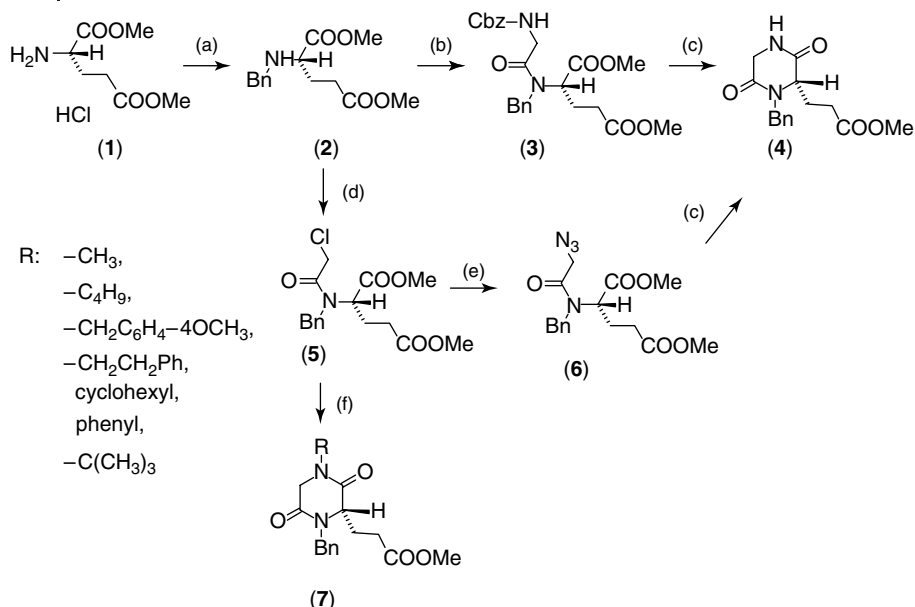
Substituted piperazines with defined configuration of the substituents are synthesized in most cases starting from enantiomerically pure starting materials. A method quite frequently applied for synthesis of piperazine ring is intramolecular amide coupling between amino and carboxylic acid ester moieties, resulting in ketopiperazines, which can be further functionalized. Further widely employed reactions for cyclization are intramolecular nucleophilic substitution, imine formation or cycloaddition. Asymmetric transformations of the piperazine ring could also be accomplished by alkylations with various electrophilic or nucleophilic reactants.

##### 7.1.3.1 Formation of the Piperazine Ring

**Ring Closure by Lactam Formation** The following scheme presents three approaches for the synthesis of diketopiperazines (DKPs) via key intermediates *N*-monobenzylglutamate **2** (prepared from dimethyl glutamate **1**) and chloroacetamide **5**.

In the first approach, *N*-benzyl-protected derivative **2** was transformed to dipeptide **3**, and subsequently cyclized to piperazine derivative **4**. As an alternative pathway to **4**, compound **2** was acylated with chloroacetyl chloride to **5**, which was





Reagents and conditions: (a)  $1. \text{C}_6\text{H}_5\text{CHO}/\text{NEt}_3/\text{pentane}/\text{Na}_2\text{SO}_4/\text{rt}$  (91%),  
 2.  $\text{NaBH}_4/\text{MeOH}/0^\circ\text{C}$  (93%),  
 (b)  $\text{Cbz-glycine}/\text{DCC}/\text{THF}/\text{CH}_2\text{Cl}_2/\text{rt}$ ,  
 (c)  $\text{H}_2/\text{Pd-C}/\text{MeOH}/\text{rt}$  (84% from 3, 87% from 6),  
 (d)  $\text{ClCH}_2\text{COCl}/\text{NaHCO}_3/\text{CH}_2\text{Cl}_2/\text{rt}$  (73%),  
 (e)  $\text{NaN}_3/\text{acetone}/\text{rt}$  (99%),  
 (f)  $\text{RNH}_2/\text{CH}_3\text{CN}$  in case of cyclohexylamine:  $\text{CH}_3\text{CN}/48 \text{ h}/\text{reflux}$ ,  
 in case of aniline:  $\text{DMF}/16 \text{ h}/155^\circ\text{C}$  (52–97%).

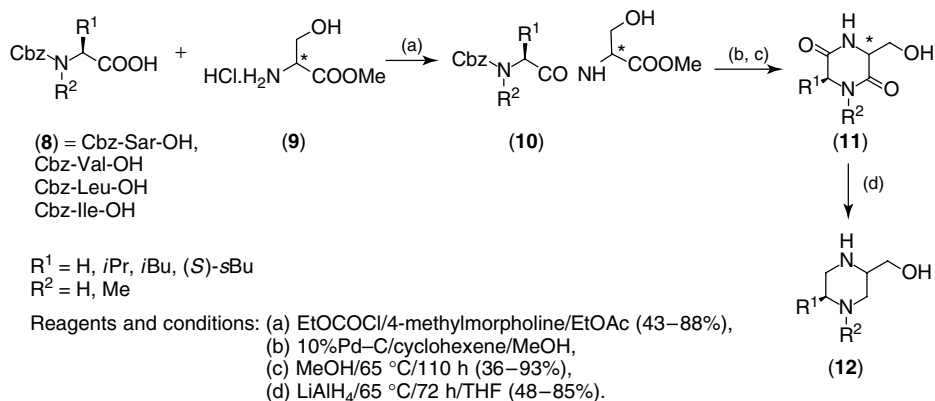
**Scheme 7.35**

reacted with  $\text{NaN}_3$ , and the azide 6 formed was hydrogenated to afford piperazine 4. According to the third approach, the chloroacetyl derivative 5 was treated with various primary amines, resulting in the cyclized products 7 in one pot [48].

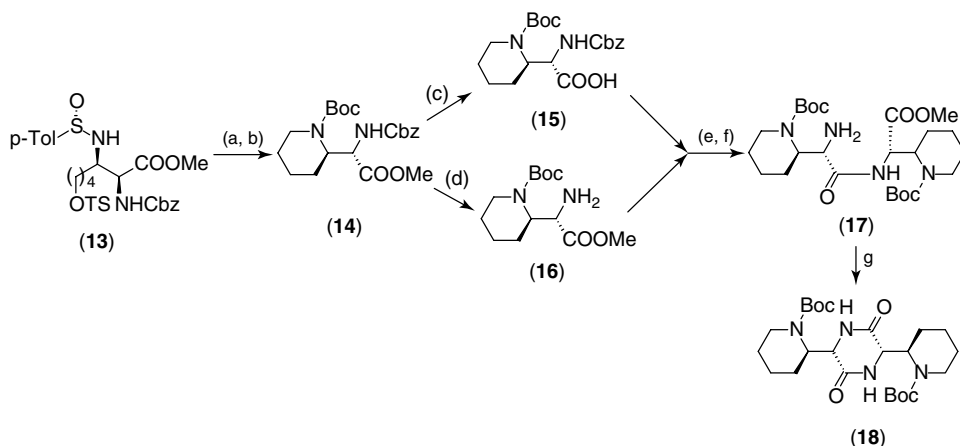
Principally in the same way as in the first approach above, a series of (2*R*,5*S*)- and (2*S*,5*S*)-2-hydroxymethyl-5-alkylpiperazines can be prepared starting from enantiomerically pure serine without any racemization. Commercial amino acids were converted into the corresponding *N*-benzyloxycarbonyl derivatives 8, which were treated with (*S*)- or (*R*)-serine methyl ester hydrochloride (9) to give dipeptides 10 via the mixed anhydride coupling method. After deblocking of the benzyloxycarbonyl group, DKPs were formed in dry methanol by heating ( $65^\circ\text{C}$ ) for five days. DKPs 11 were reduced to piperazines 12 with an excess of  $\text{LiAlH}_4$  in refluxing THF [49].

DKP 18 was synthesized from *N*-sulfinyldiamino ester 13 via dipeptide 17, which was prepared by coupling of the differently protected derivatives 15 and 16 of the same amino acid [50].

Dilactim ethers 22, known as Schöllkopf chiral auxiliaries widely used for asymmetric synthesis of amino acids, were prepared from amino acids 19 in



Scheme 7.36

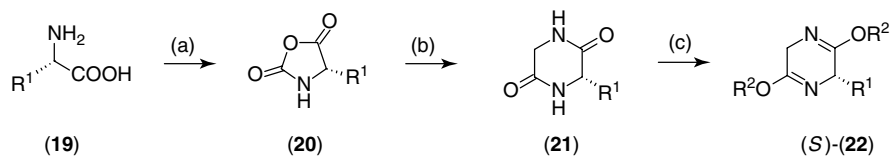


Reagents and conditions: (a) 1.  $\text{H}_3\text{PO}_4/\text{MeOH}/\text{H}_2\text{O}$ , 2.  $\text{K}_2\text{CO}_3$ , (b)  $\text{Boc}_2\text{O}/\text{Et}_3\text{N}/\text{dioxane}/\text{H}_2\text{O}$  (82%),  
(c)  $\text{LiOH}/\text{THF}/\text{H}_2\text{O}$  (100%), (d)  $\text{Pd}-\text{C}/\text{H}_2$  (100%), (e)  $\text{BOP}/\text{DIPEA}/\text{CH}_2\text{Cl}_2$ ,  
(f)  $\text{Pd}-\text{C}/\text{H}_2$  (85% 2 steps), (g)  $\text{DMF}/\text{rt}/40\text{ h}$  (22%)  
or  $\text{KCN}/\text{DMF}/80\text{ }^\circ\text{C}/4\text{ d}$  (29%).

Scheme 7.37

three steps. Reaction with triphosgene was followed by treatment of the resulting oxazolidinone **20** with ethyl glycinate to give piperazinedione **21**, which was subsequently transformed to dilactim ether **22** [51, 52]. The enantiomer of **22** could also be prepared via the same route starting from the enantiomer of the corresponding amino acid [53–55].

Synthesis of the naturally occurring DKPs (–)-phenylhistine (**28**,  $R = \text{Bn}$ ) and (–)-aurantiamine (**28**,  $R = i\text{Pr}$ ) begins with the coupling of amino acid **23** and phosphinyl glycine **24**. Phosphinyl ester dipeptide **25** was then reacted with formylimidazole **26** under Horner–Emmons coupling conditions. Finally, *in situ*

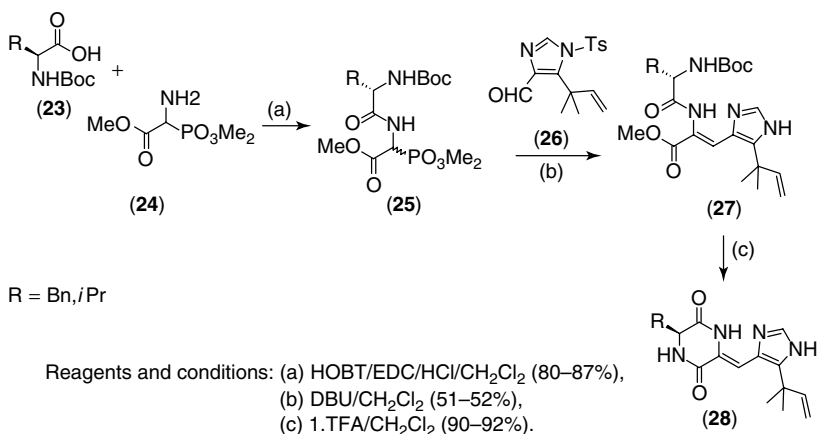


$R^1 = i\text{Pr, tBu}$

$R^2 = \text{Me, Et}$

Reagents and conditions: (a) triphosgene/THF (99%), (b) 1.  $\text{NH}_2\text{CH}_2\text{CO}_2\text{Et}/\text{CHCl}_3/\text{EtN}_3/\text{THF}/-70^\circ\text{C}$ , 2. toluene or xylene/rfx (70%), (c)  $\text{R}_2^3\text{OBF}_4/\text{CH}_2\text{Cl}_2$  (90%).

Scheme 7.38



$R = \text{Bn, } i\text{Pr}$

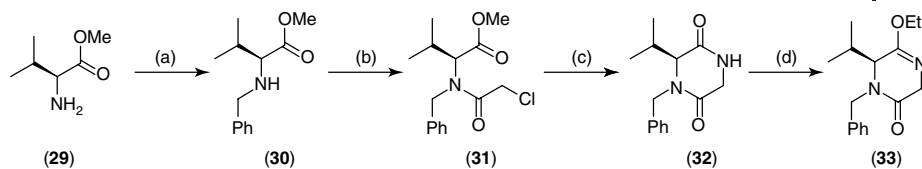
Reagents and conditions: (a) HOBT/EDC/HCl/ $\text{CH}_2\text{Cl}_2$  (80–87%), (b) DBU/ $\text{CH}_2\text{Cl}_2$  (51–52%), (c) 1. TFA/ $\text{CH}_2\text{Cl}_2$  (90–92%).

Scheme 7.39

ring closure of **27**, during hydrolysis of the Boc-protecting group, resulted in the products **28** [56].

Analogous to the second approach shown in Scheme 7.35, ethyl or menthyl (2*S*)-5,6-dioxo-4-[(1*R*)-1-phenylethyl]piperazine-2-carboxylates were synthesized starting with ring opening of ethyl or menthyl (2*R*)-1-[(1*R*)-1-phenylethyl]aziridine-2-carboxylate with azide as nucleophile in aqueous acidic media in the presence of a catalytic amount of  $\text{AlCl}_3 \cdot 6\text{H}_2\text{O}$ , furnishing stereoselectively the corresponding (2*S*)-2-azido-3-[(1*R*)-1-phenylethyl]aminopropanoates, which were made to react with methyl oxalyl chloride, followed by catalytic hydrogenation. The absolute configuration, determined by X-ray crystallography, showed that the ring opening proceeded with complete inversion at the reaction center [57].

Monolactim ether **33**, widely used by Sandri *et al.* as a chiral auxiliary in syntheses of amino acids, was prepared according to the third approach shown in Scheme 7.35. L-Valine methyl ester (**29**) was benzylated to **30**, followed by N-acylation with chloroacetyl chloride. Ester hydrolysis of **31** and cyclization with ammonia gave **33** after treatment of **32** with  $\text{Et}_3\text{OBF}_4$  [58].



Reagents and conditions: (a)  $\text{PhCH}_2\text{Br}$ /pyridine/ $\text{CH}_2\text{Cl}_2$  (85%), (b)  $\text{ClCH}_2\text{COCl}$ /TEA/ $\text{CH}_2\text{Cl}_2$  (96%), (c) 10 M  $\text{NH}_3$  in EtOH (>98%), (d)  $\text{EtO}_3\text{BF}_4$ / $\text{CH}_2\text{Cl}_2$  (75%).

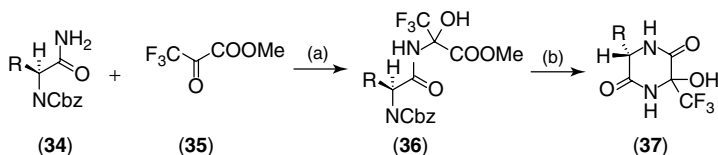
Scheme 7.40

Applying the third approach shown in Scheme 7.35, piperazino-piperidine-based CCR5 antagonists were synthesized via reductive amination of 4-trifluoromethylacetophenone with various L-amino acids, followed by N-acylation with chloroacetyl chloride, and subsequent cyclization in the presence of 1-Boc-protected-4-substituted-4-aminopiperidines [59].

By the same strategy, the four possible stereoisomers of the *N*-acetyl derivative of the natural marine compound Etzionin were synthesized to carry out a stereochemical analysis by comparing the natural compound and the stereoisomers synthesized from enantiomerically pure starting materials. Thus, for synthesis of the (*S,R*) diastereomer, methyl (2*S*)-2-[(bromoacetyl)amino]-3-phenylpropanoate was submitted to nucleophilic displacement with methyl (3*R*)-3-aminododecanoate to give the corresponding peptide and subsequently cyclized [60].

DKPs **37** were prepared from protected amino acid amides **34** by the addition to methyl 3,3,3-trifluoropiruvate (**35**). The adduct dipeptides **36** were then converted to the corresponding 3-hydroxy-3-trifluoromethyl-2,5-diketopiperazines **37**, which are used as homochiral electrophilic synthons for  $\alpha$ -trifluoromethyl amino acids [61].

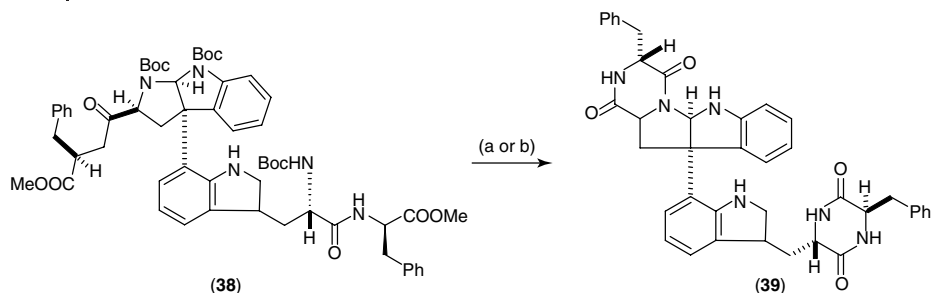
The last step in the total synthesis of the cyclotryptophan alkaloid asperazine (**39**) is the formation of two DKP rings. A series of five reactions could be accomplished in a single step by heating **38** at 200 °C under argon. The reaction gave **39** and two stereoisomers in 70:3:2 ratio; after separation, **39** was obtained in 34% yield. However, the conversion of **38** to **39** was more efficient when two separate steps were applied. First, removal of the Boc-protecting groups, followed by heating of the crude deprotected reaction mixture in butanol in the presence of acetic acid, gave **39** in 59% yield [62].



R = Me, *i*Pr, *i*Bu, Bzl

Reagents and conditions: (a)  $\text{CH}_2\text{Cl}_2$ , (b)  $\text{H}_2$ /Pd-C/MeOH (69–86%).

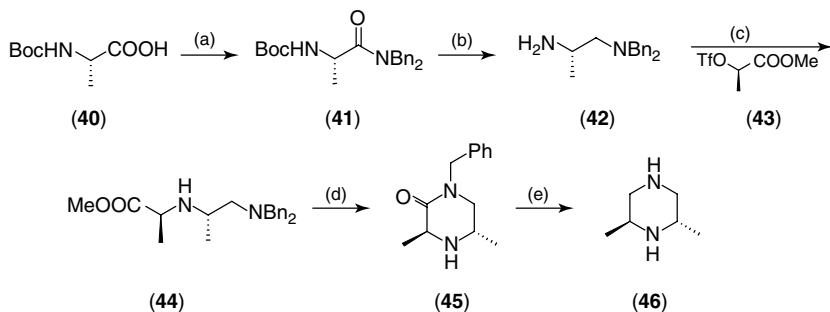
Scheme 7.41



Reagents and conditions: (a) 200 °C, 4h (34%), (b) 1. HCOOH, 2. AcOH, *n*BuOH, 120 °C (59%).

**Scheme 7.42**

Analogous to DKP formation, monoketopiperazines are synthesized via intramolecular amide coupling of *N*-aminoethyl substituted amino acids. Thus, enantiomerically pure 2,6-dimethylpiperazin-5-ones **45** were synthesized by employing a diastereoselective triflate alkylation to set the required stereochemistry. The reaction sequence started with the conversion of *N*-Boc-L-alanine (**40**) to dibenzylamide (**41**) through the mixed anhydride. Removal of the Boc group, followed by borane-methyl sulfide reduction, gave diamine **42**, which was alkylated with the triflate (**43**) of methyl (*R*)-lactate. The alkylation proceeded with inversion to afford ester **44**. Hydrogenolysis of **44** in the presence of HCl resulted in monodebenzylation and partial cyclization, which was completed by heating in the presence of *p*-toluenesulfonic acid to ketopiperazine **45**. Reduction of the oxo group with  $\text{LiAlH}_4$ , followed by debenzylization with Pearlman's catalyst, gave



Reagents and conditions: (a) 1.  $\text{ClCOO}i\text{Bu}/\text{Et}_3\text{N}/\text{THF}$ , 2.  $\text{Bn}_2\text{NH}$  (82%),  
 (b) 1. TFA/ $\text{CH}_2\text{Cl}_2$ ,  
 2.  $\text{BH}_3\cdot\text{DMS}/\text{THF}$  (84% for 2 steps, 98% ee),  
 (c)  $\text{CH}_2\text{Cl}_2/\text{Et}_3\text{N}$  (94%),  
 (d) 1.  $\text{Pd}-\text{C}/\text{H}_2/\text{HCl}/\text{EtOH}$ , 2.  $\text{TsOH}/\text{EtOH}/\text{rfx}$  (81%),  
 (e)  $\text{LiAlH}_4/\text{THF}$  (93%, 98% ee),  
 (f)  $\text{Pd}(\text{OH})_2/\text{H}_2/\text{MeOH}$  (91%, 98% ee).

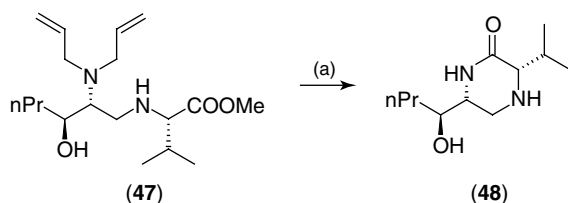
**Scheme 7.43**

(2*S*,6*S*)-2,6-dimethylpiperazine (**46**). The (*R,R*) enantiomer was prepared in an analogous way from *N*-Boc-D-alanine and methyl (*S*)-lactate [63, 64].

*N*-(2-Diallylamino-3-hydroxyalkyl)-substituted amino acid esters were deallylated to primary amines under mild conditions with  $(\text{PPh}_3)_3\text{RhCl}$ . While *tert*-butyl esters could be easily deprotected to the corresponding primary amine, methyl esters such as **47** spontaneously cyclized to piperazine **48** after deprotection [65].

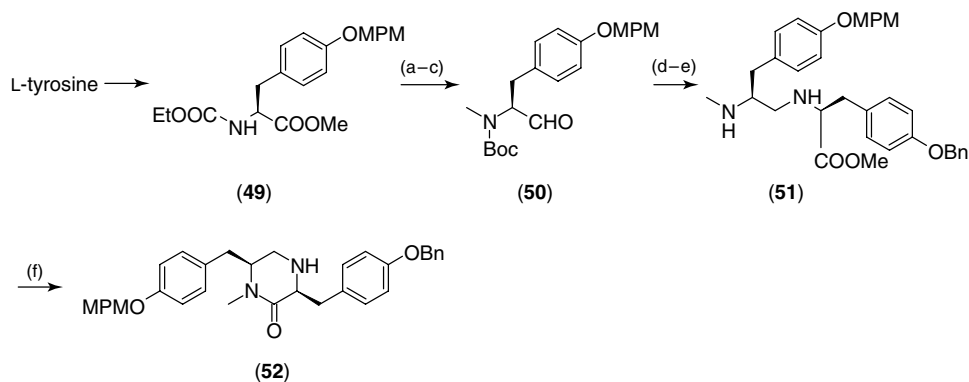
As a building block for the synthesis of natural products TAN1251C and D, disubstituted piperazine **32** was synthesized from carbamate **49** obtained from L-tyrosine. Reduction of **49** with  $\text{LiAlH}_4$ , followed by Boc protection and subsequent Swern oxidation of the corresponding primary alcohol, gave aldehyde **50**, which was condensed with *O*-benzyl-L-tyrosine under reductive conditions. After deprotection of the Boc group, amine **51** was cyclized with NaOMe to piperazinone **52** [66].

Piperazine-2-carboxylic acid ester enantiomers **57** were prepared from L- or D-serine ester **53** via the azide intermediate **54**, obtained by Mitsunobu reaction. After deprotection of **54**, the amino compound was alkylated with the triflate (**55**) of dimethyl-D-malate to afford L-aspartic acid derivative **56** via an  $\text{S}_{\text{N}}2$  reaction. Reduction of the azido group in **70** resulted in spontaneous lactam formation to piperazine derivative **57** [67].



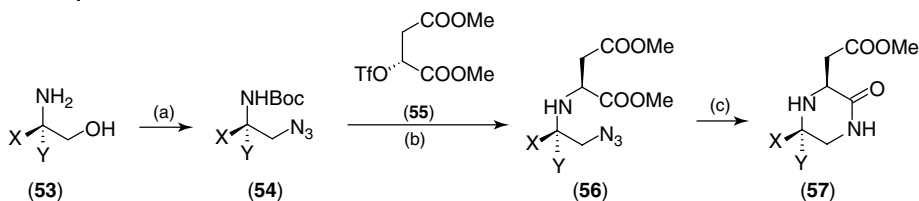
Reagents and conditions: (a)  $(\text{PPh}_3)_3\text{RhCl}/\text{MeCN}/\text{H}_2\text{O}$  (47%).

Scheme 7.44



Reagents and conditions: (a)  $\text{LiAlH}_4/\text{THF}$  (82%), (b)  $\text{Boc}_2\text{O}/\text{THF}-\text{H}_2\text{O}$  (99%), (c)  $(\text{COCl})_2/\text{DMSO}/\text{Et}_3\text{N}$ , (d) *O*-Bn-L-tyrosine methyl ester/ $\text{NaBH}_3\text{CN}/\text{DMF}$  (90%), (e)  $\text{ZnBr}_2/\text{CH}_2\text{Cl}_2$  (99%), (f)  $\text{NaOMe}/\text{THF}$  (85%).

Scheme 7.45



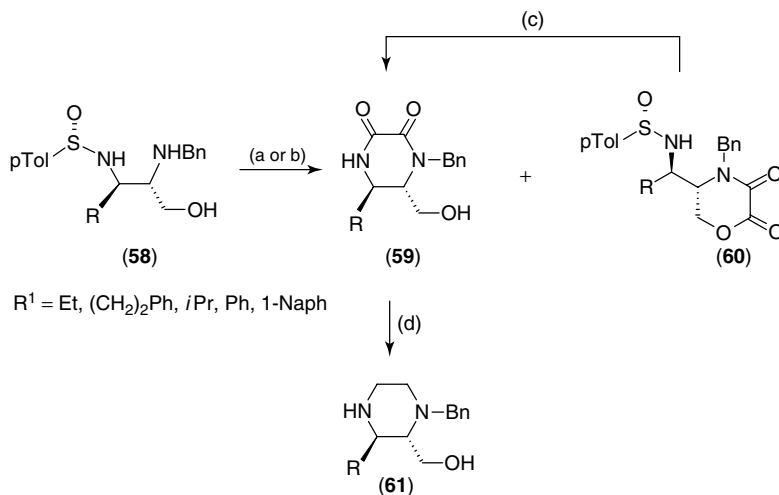
X = Cbz, Y = H or X = H, Y = Cbz

Reagents and conditions: (a) 1.  $\text{Boc}_2\text{O}/\text{H}_2\text{O}/\text{dioxane}$ , 2.  $\text{HN}_3/(i\text{PrNOOC})_2/\text{PPh}_3$  (39–67%),  
 (b) 1.  $\text{TFA}/\text{CH}_2\text{Cl}_2$ , 2.  $55/\text{CH}_2\text{Cl}_2/2,6\text{-lutidine}$  (61–73%),  
 (c)  $\text{PPh}_3/\text{THF}$  (49–85%).

Scheme 7.46

Viso *et al.* employed chiral sulfinamides for the synthesis of enantiomerically pure substituted piperazines. 1-Benzyl-2,3-disubstituted piperazines **61** were obtained by treatment of *N*-sulfinyl-*N*-benzylamino alcohols **58** with diethyl oxalate and NaOMe, followed by borane reduction. Ring closure of **58** gave morpholine derivative **60** as a side-product, which could be transformed to piperazine **59** by NaOMe treatment [68, 69].

(2*S*,3*S*)-2,3-bis[(benzyloxy)methyl]piperazine was prepared from (*S,S*)-threitol-1,4-dibenzyloxy ether also via a 1,2-diamino intermediate by a five-step reaction



Reagents and conditions: (a)  $(\text{COOEt})_2/\text{NaOMe}/\text{CH}_2\text{Cl}_2/\text{MeOH}$ ,  
 (b) 1.  $(\text{COOEt})_2/\text{CH}_2\text{Cl}_2$   
 2.  $\text{NaOMe}/\text{MeOH}$  (77–90% for **59**, 10–15% for **60**),  
 (c)  $\text{NaOMe}/\text{MeOH}$ ,  
 (d)  $\text{BH}_3\cdot\text{DMS}/\text{THF}$  (60–84%).

Scheme 7.47

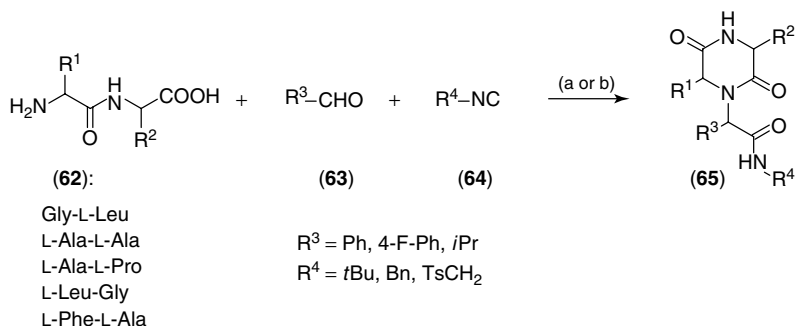
sequence: (i) mesylation, (ii) nucleophilic displacement with azide, (iii)  $\text{LiAlH}_4$  reduction, (iv) cyclization with diethyl oxalate, and finally (v) reduction of the oxo groups [70].

2,5-Diketopiperazine derivatives **65** were synthesized through Ugi four-center three-component reactions from commercially available dipeptides **62**, aldehydes **63**, and isocyanides **64** in 2,2,2-trifluoroethanol as solvent in moderate to good yields. A new chiral center was created at the carbon originating from the aldehyde; the relative stereochemistry of the resulting diastereomers was not determined. The best observed diastereomeric ratio was 6:1. The reaction time and yield could be improved by the application of microwave irradiation [71].

Trisubstituted DKPs were synthesized by intramolecular amidation of dipeptide esters, obtained in four-component Ugi reactions. Thus, the imine intermediate **67** formed *in situ* from (*R*)-leucine methyl ester (**66**) and benzaldehyde was reacted with *tert*-butylisocyanide and (*R*)-indanyl glycine **68**. The dipeptide ester **69** formed was then treated with 4 N HCl in dioxane, which resulted in removal of the Boc-protecting group and partial cyclization, which was completed by addition of triethylamine to give a 1:3 mixture of diastereomers **70** and **71**. The partial stereocontrol originates from the attack of the isocyanide on the less hindered face of the imine [72].

As an alternative route to isomeric DKPs, secondary amine **95** was prepared first via a four-center three-component Ugi reaction and subsequent hydrolysis. Then it was acylated with (*R*)-Boc-indanyl glycine **91** through mixed anhydride **96**. Dipeptide intermediate **97** was then cyclized to **98** [73].

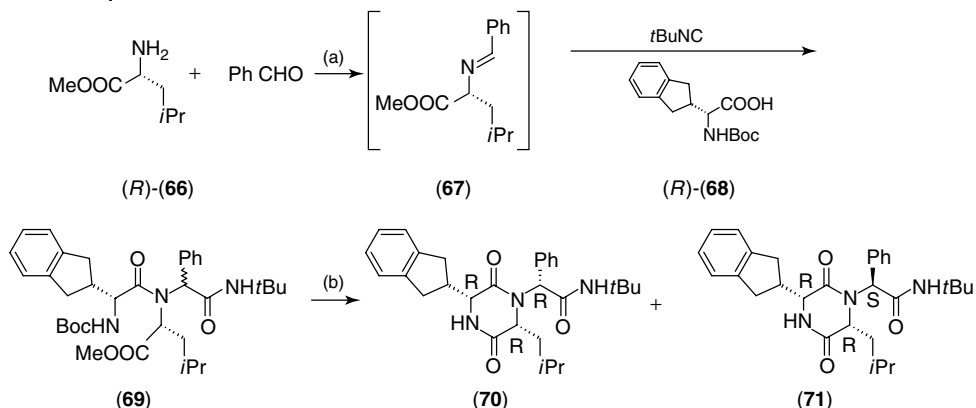
**Ring Closure by Intramolecular Nucleophilic Substitution** O-protected *N*-sulfinyl diaminoalcohols **76** were acylated with chloroacetyl chloride to **77** and subsequently cyclized to *N*-sulfinylpiperazines **78**. The sulfinyl group was eliminated by treatment with NaH, affording unsaturated derivative **79** [69].



Reagents and conditions: (a)  $-40^\circ\text{C}$  to rt/  $\text{CF}_3\text{CH}_2\text{OH}$ /33–52 h (24–87%, dr 2:1 to 6:1) or  
 (b) MW (30 W)  $100^\circ\text{C}$ / $\text{CF}_3\text{CH}_2\text{OH}$ -BmimPF<sub>6</sub>/15 min  
 (42–58%, dr 2:1 to 3:1).

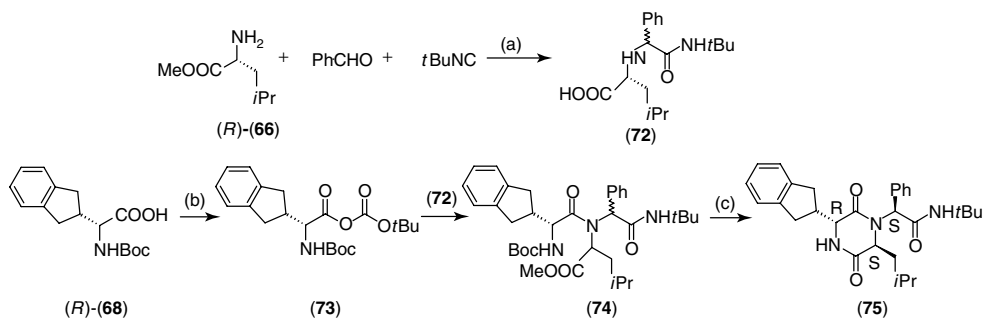
Scheme 7.48





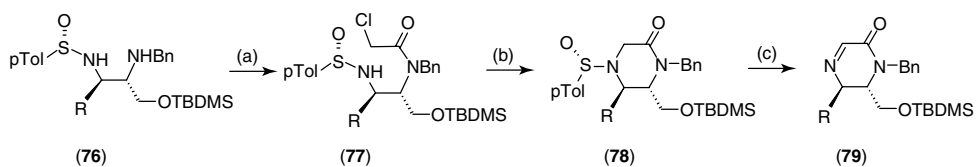
Reagents and conditions: (a) Et<sub>3</sub>N/MeOH, (b) 1. 4 N HCl/dioxane, 2. Et<sub>3</sub>N/dioxane.

Scheme 7.49



Reagents and conditions: (a) MeOH/−30 °C to rt, (b) *i*PrOCOCi/N-Me-morpholine/THF, (c) 1.4 N HCl/dioxane, 2. HCl/MeOH (57%).

Scheme 7.50



R<sup>1</sup> = Et, (CH<sub>2</sub>)<sub>2</sub>Ph, *i*Pr, Ph, 1-Naph

Reagents and conditions: (a) ClCH<sub>2</sub>COCi/EtOAc:NaHCO<sub>3</sub> (1:1) satd, (52–90%), (b) Cs<sub>2</sub>CO<sub>3</sub>/DMF (74–92%), (c) NaH/THF (73–87%).

Scheme 7.51

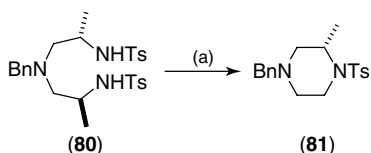
1-Benzyl 2-methyl (2S,3R)-3-alkyl-5-oxopiperazine-1,2-dicarboxylates were prepared in an analogous way from 1N-*p*-tolylsulfinyl derivative of methyl (2R,5R)-5-methyl-2-phenylimidazolidine-4-carboxylate [50].

A diamino derivative was cyclized to piperazine in an unexpected way in the following reaction. The treatment of bistosylamide **80** with ethylene glycol ditosylate did not give the expected Richman–Atkins cyclization. Instead, chiral piperazine **81** was formed as a result of nucleophilic attack of the central benzylic amine on the electrophilic tosylate in ethylene glycol ditosylate, followed with expulsion of the C-3 tosamide unit either before or during the cyclization [73].

Although, generally, Mitsunobu reactions involving a nitrogen nucleophile require an acidic hydrogen ( $pK_a < 13$ ), there are examples of intramolecular Mitsunobu reactions of amino alcohols to obtain heterocycles. Accordingly, cyclization of **85** by treatment with  $PPh_3$ /diethyl azodicarboxylate (DEAD) resulted in benzylated piperazine **86**. Amino alcohol **85** was prepared from (*R*)-1-aminopropan-2-ol (**82**) by reductive alkylation and the subsequent coupling of **83** with *N*-Boc-L-alanine providing **84**, which was reduced to **85** [63].

The method could be extended to the preparation of monomethylpiperazines. The first step was the coupling of *N*-Boc-D-alanine (**87**) with *N*-benzylethanolamine to amide **88**. Subsequent hydrolysis of the Boc group followed by the Mitsunobu reaction gave methylpiperazinone **89**, which was reduced to methylpiperazine **90** [63].

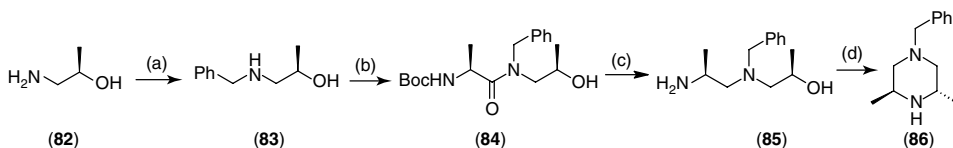
**Cyclization via Imine/Enamine Formation** The synthesis of tetrahydropyrazinone **93** was based on the coupling of  $\alpha$ -aminoketone **91** with *N*-Boc-L-alanine pivalic acid mixed anhydride to **92**. Compound **91** was obtained from (*R*)-valine in a three-step reaction sequence (i) *N*-protection with Boc, (ii) transformation of the carboxylic group to dimethyl amide, followed by (iii) reaction with phenylmagnesium bromide. After acidic deprotection of **92**, the pyrazine ring was formed by intramolecular



Reagents and conditions:

- (a) 1. NaH/THF/ $\Delta$ ,  
2.  $(CH_2OTs)_2$ /DMF/120 °C (32%).

Scheme 7.52

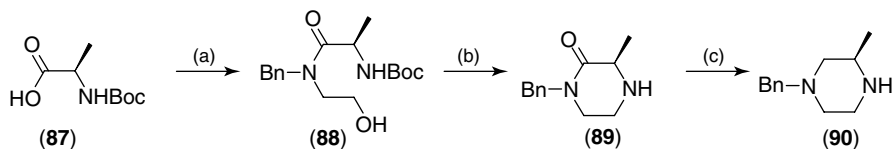


Reagents and conditions: (a) 1.  $PhCHO/MgSO_4$ /THF, 2.  $NaBH_4$ /EtOH (57%),

(b)  $CDI/CH_2Cl_2$ /*N*-Boc-L-Alanine (80%),

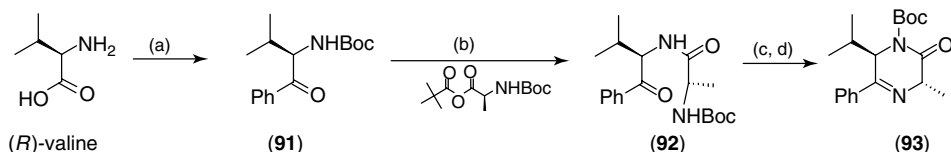
(c) 1. TFA/ $CH_2Cl_2$ , 2.  $BH_3 \cdot DMS$ /THF (76%, 2 steps), (d) DEAD/ $PPh_3$ /THF (66%).

Scheme 7.53



Reagents and conditions: (a) CDI/CH<sub>2</sub>Cl<sub>2</sub>/N-benzyl-ethanolamine (81%), (b) 1. TFA/CH<sub>2</sub>Cl<sub>2</sub>,  
2. DEAD/PPH<sub>3</sub>/THF (62%),  
(c) LiAlH<sub>4</sub>/THF (88%).

Scheme 7.54



Reagents and conditions: (a) 1. (Boc)<sub>2</sub>O, 2. Me<sub>2</sub>NH·HCl/TBTU,  
3. PhMgBr (78%), (b) HCl<sub>g</sub>/EtOAc (95%),  
(c) 1. HCl<sub>g</sub>/EtOAc, 2. K<sub>2</sub>CO<sub>3</sub> (86%),  
(d) (Boc)<sub>2</sub>O/0 °C/THF (84%, *trans*:*cis* = 20:1).

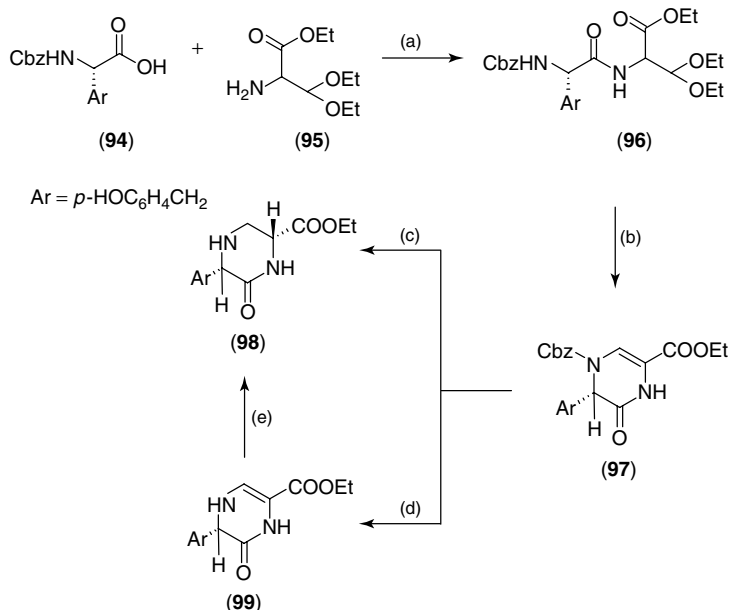
Scheme 7.55

condensation between the oxo and amino groups, which was transformed to Boc-protected derivative **93** as a 20:1 mixture of the *trans* and *cis* diastereomers [74, 75]. In an analogous way, a derivative of **121** without methyl substituent was also prepared using *N*-Boc-glycine pivalic acid mixed anhydride instead of alanine derivative as the coupling partner of **119** [76].

Synthesis of piperazinecarboxylic ester **98** was achieved by starting with the coupling of protected L-tyrosine **94** and 2-amino-3,3-diethoxypropionate (**95**). The dipeptide **96** obtained was then cyclized to unsaturated piperazine **97** by treatment with TFA. Subsequent catalytic hydrogenation under acidic conditions resulted selectively in the single diastereomer **98**. When the acid was omitted, no reduction of the double bond occurred, and **99** was isolated, which could be reduced to **98** with NaCNBH<sub>3</sub> in the presence of HCl [77].

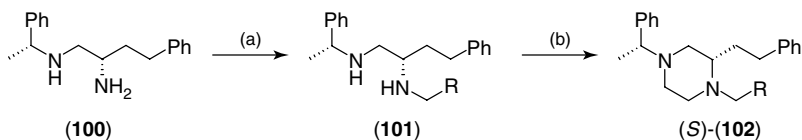
Reaction of the primary amino moiety in **100** with aldehydes and subsequent reduction of the imine intermediate with NaBH<sub>4</sub> gave alkylamino derivatives **101**. Reductive cyclization of **101** with aqueous glyoxal solution in the presence of NaCNBH<sub>3</sub> as reducing agent provided 2-substituted-1,4-piperazines **102** [78].

Diastereomeric 3,5-disubstituted piperazines **104** and **105** were formed in high yields but in moderate ratios when the corresponding β-keto esters **103** were hydrogenated at 45 °C and 45 psi with Pd/C as catalyst. Removal of the Cbz protecting group and reductive amination took place in a one-pot reaction. Although in slightly lower yield, the piperazine ring was also formed in two steps involving



Reagents and conditions: (a) DCC/HOBT/CH<sub>2</sub>Cl<sub>2</sub> (100%),  
 (b) TFA/H<sub>2</sub>O (70%),  
 (c) Pd(OH)<sub>2</sub>/H<sub>2</sub>/HCl then neutr. (70%),  
 (d) Pd(OH)<sub>2</sub>/H<sub>2</sub>/EtOH,  
 (e) NaCNBH<sub>3</sub>/HCl/MeOH (70%).

Scheme 7.56



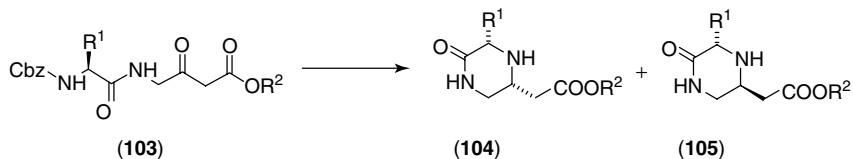
R = Ph, pentyl

Reagents and conditions: (a) 1. RCHO/MgSO<sub>4</sub>/MeOH, 2. NaBH<sub>4</sub> (83–94%),  
 (b) (CHO)<sub>2</sub>/NaCNBH<sub>3</sub>/MeOH (85–87%).

Scheme 7.57

removal of the Cbz group, by catalytic hydrogenation and reduction of the resulting intermediates with NaBH<sub>3</sub>CN in the presence of ZnCl<sub>2</sub> [79].

The enantioselective synthesis of the antipode (111) of the pyrazinone alkaloid hamacanthin A was based on Sharpless asymmetric dihydroxylation of vinylindole **106** with asymmetric dihydroxylation (AD)-mix- $\alpha$  to give (*S*)-indolyl-1,2-ethanediol **107**, which was then transformed to 3-indolylazidoethylamine **108** in seven steps. Compound **108** was coupled with 6-bromo-3-indolyl- $\alpha$ -oxoacetyl chloride to azide

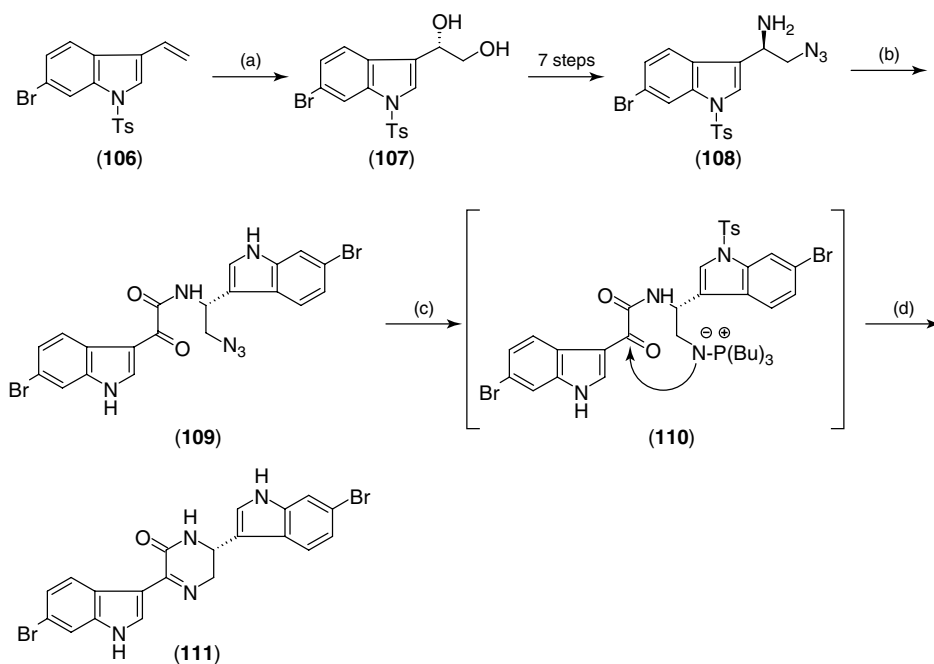


$R^1 = \text{Me, Bn}$   
 $R^2 = \text{Me, Et}$

Reagents and conditions: Method A:  $\text{H}_2/\text{Pd-C}$ , 45 psi, 45 °C, 48–72 h (89–97%);  
 Method B: 1.  $\text{H}_2/\text{Pd-C}/25^\circ\text{C}/2\text{ h}$ , 2.  $\text{NaBH}_3\text{CN}/\text{ZnCl}_2/25^\circ\text{C}/3\text{ h}$  (64–80%)  
 (dr 1.7:1 to 5.7:1).

Scheme 7.58

**109**, followed by an intramolecular Staudinger-aza-Wittig cyclization through intermediate **110** [80]. For the synthesis of the related alkaloids hamacanthin A [81], hamacanthin B [81, 82], antipode of *cis*-dihydrohamacanthin B [81, 83], and the antipode of *cis*- and *trans*-dihydrohamacanthin A [84], a similar approach was applied.



Reagents and conditions: (a) AD-mix- $\alpha$  (92%),  
 (b) 6-bromo-3-indolyl- $\alpha$ -oxoacetyl chloride/ $\text{Et}_3\text{N}/\text{DMF}$  (74%),  
 (c) 1.  $n\text{Bu}_3\text{P}/\text{toluene}/\text{r.f.}$ , 2. reflux (97%), (d)  $\text{NaOH}/\text{MeOH}/\text{r.f.}$  (88%).

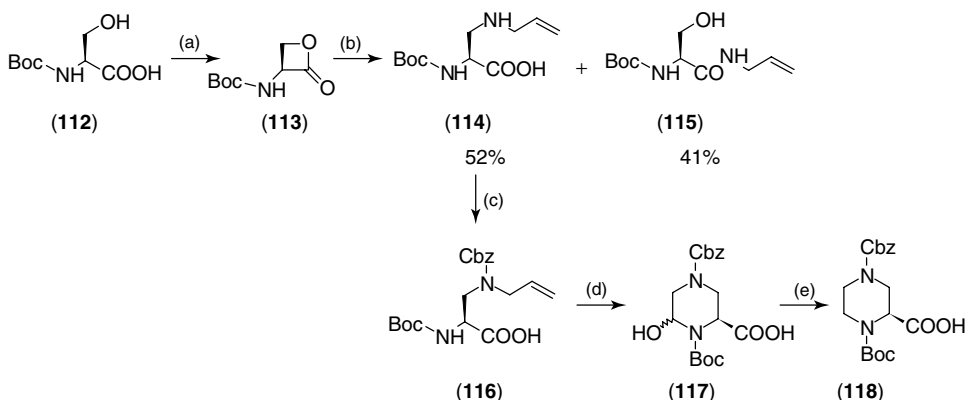
Scheme 7.59

Piperazine-2-carboxylic acid is a conformationally restricted nonproteinogenic amino acid with medicinal applications. It is widely used as a building block in a number of bioactive compounds [85–87].

Synthesis of orthogonally protected (S)-piperazine-2-carboxylic acid **118** has been achieved in four steps from *N*-Boc-L-serine  $\beta$ -lactone **113**, obtained from protected L-serine **112** via a Mitsunobu reaction, by utilizing an extension of the Vederas' serine lactone ring-opening methodology. Thus, treatment of lactone **113** with allylamine gave a mixture of amino acid **114** and amide **115**. Cbz protection of **114** to **116** and subsequent ozonolysis gave piperazine **117** via the corresponding formyl intermediate. Compound **117** was then reduced chemoselectively to (S)-piperazinecarboxylic acid derivative **118** [88].

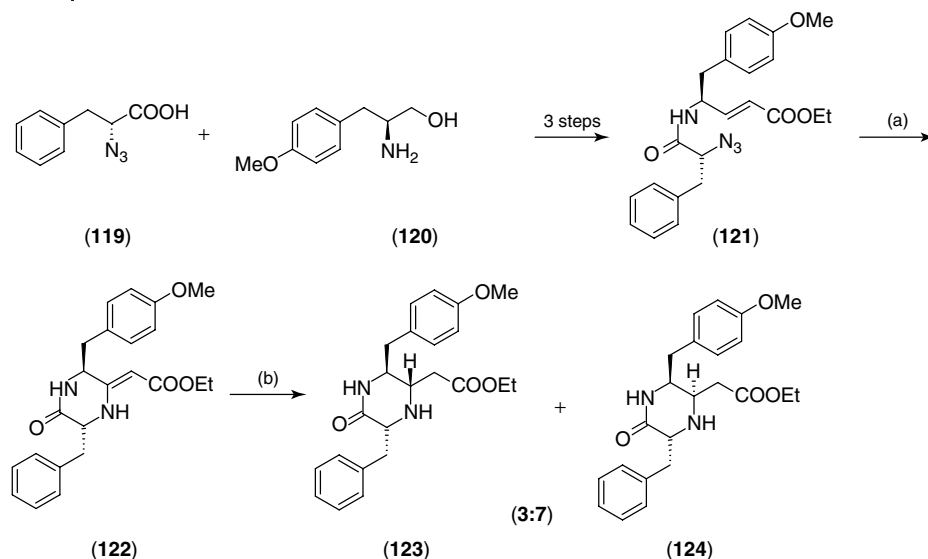
**Cycloaddition** The key step for the synthesis of the piperazinone ring system of pseudotheonamide  $A_1$  (**123**) and  $A_2$  (**124**) was intramolecular [3 + 2] cycloaddition of the appropriately oriented azido group and the  $\alpha,\beta$ -unsaturated ester moiety in compound **121**, which was obtained from (*R*)- $\alpha$ -azido acid **119** and *p*-aminophenylalaninol **120** in three steps. The target molecules were then obtained as a 3:7 mixture of the corresponding diastereomers by reduction of **122** [89].

Similarly, enantiomerically pure piperazines were prepared via intermolecular [3 + 2] cycloaddition of an azide to a C–C double bond in *N*-allyl-1,2-azidoamines, which were prepared from 1,2-amino alcohols. The corresponding cycloadduct triazolopyrazine derivative was then reacted with acyl chlorides, carbamoyl chlorides, or alkyl halides to obtain halomethylpiperazines [90, 91].



Reagents and conditions: (a) DEAD/ $\text{Ph}_3\text{P}$ /THF, (b)  $\text{CH}_2=\text{CHCH}_2\text{NH}_2/\text{MeCN}$ , (c) CbzCl/ $\text{NaHCO}_3/\text{H}_2\text{O}$ /acetone (97%), (d) 1.  $\text{O}_3$ , 2.  $\text{Me}_2\text{S}$ , (e)  $\text{Et}_3\text{SiH}/\text{BF}_3(\text{OEt})_2$  (80%).

Scheme 7.60



Reagents and conditions: (a)  $\text{Et}_3\text{N}$  (catalytic)/toluene/rf (56%)

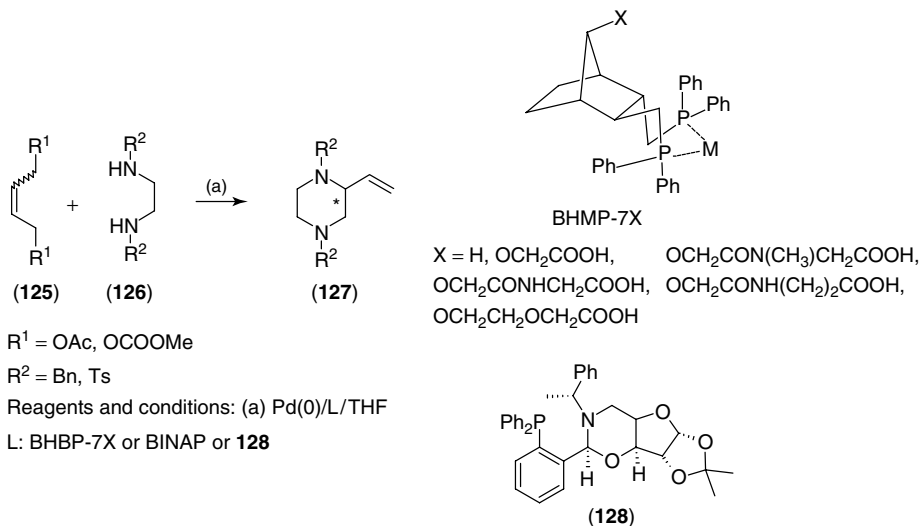
(b)  $\text{NaCNBH}_3/\text{MeOH}/5\% \text{ HCl}$  (90%).

Scheme 7.61

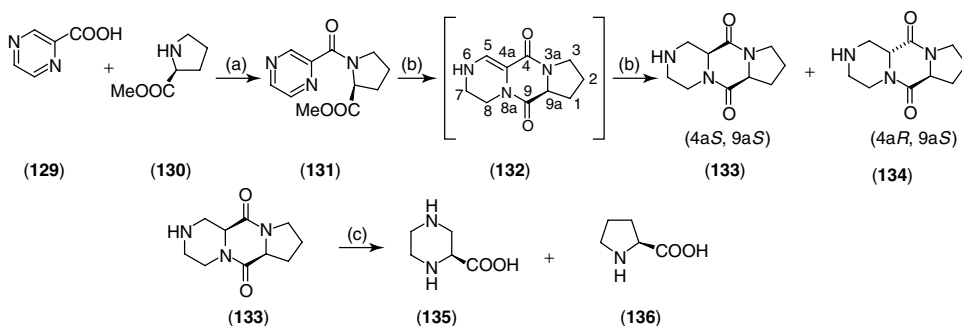
**Miscellaneous Methods for Ring Closure** The asymmetric synthesis of 2-vinylpiperazines **127** has been described from olefins **125** and 1,2-bis[benzylamino]ethane **126** in the presence of a chiral Pd(0) complex. On using  $\text{Pd}_2(\text{dba})_3$  as the Pd source and [bicyclo[2.2.1]heptane-2,3-diylbis(methylene)]bis(diphenylphosphine) (BHMP) as chiral phosphine ligand, moderate yields (28–68%) and enantioselectivities (22–42% ee) were achieved [92]. The cyclized product was obtained in 87% yield and 60% ee by the application of BINAP as ligand [93], while the combination of  $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$  and phosphinooxazinanone **162** gave vinylpiperazine **161** in 50% yield and 70% ee [94].

Kukula's method for synthesis of piperazine-(2*S*)-carboxylic acid **135** consists of three simple steps: (i) coupling of the precursor **129** with (*S*)-proline methyl ester (**130**) as a chiral auxiliary, (ii) heterogeneous diastereoselective hydrogenation of amide **131** via intermediate **132** to give diastereomers **133** and **134** in a ratio of 4:1, and (iii) acidic hydrolysis of the tricyclic amide **133**. The diastereoselectivity obtained in the hydrogenation of the substrate over a Pd catalyst was considerably higher than over Rh, Ru or Pt catalysts. Separation of the two diastereomers from the hydrogenation product by crystallization is possible [95].

With (*R*)-phenylglycinol (**137**) as the chiral inductor, 2,3-dialkyl-substituted piperazines were synthesized via hydroxyethylenediamine precursor **139**, which was obtained by reduction of oxazino-oxazine **138**. Compound **139** was condensed with  $\alpha$ -dicarbonyl compounds (glyoxal or 1-phenyl-1,2-propanedione), which afforded bisoxazolidine **140** or **143** as single diastereomers, while the reaction with



Scheme 7.62



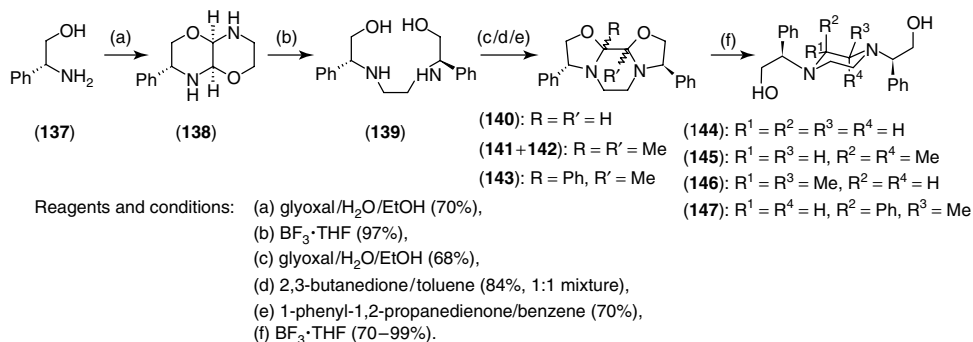
Scheme 7.63

2,3-butanedienone gave a 1:1 diastereomeric mixture of **141** and **142**. The bisoxazolidinones **140**–**143** obtained were reduced to give piperazine derivatives **144**–**147**, respectively [96].

### 7.1.3.2 Stereoselective Transformation of the Piperazine Ring

**Alkylations** Metalated bislactim ethers (known as Schöllkopf chiral auxiliaries) derived from DKPs are widely used as homochiral nucleophilic templates (homochiral glycine anion equivalents) for the synthesis of nonproteogenic  $\alpha$ -amino acids. In this approach, enantiomerically pure bislactim ethers such as (*S*)-**22** can be deprotonated with  $n\text{BuLi}$  and the aza-enolate anions **148** formed are alkylated with an alkyl halogenide as electrophile. The alkyl group  $R^3$  enters *trans* to the  $R^1$





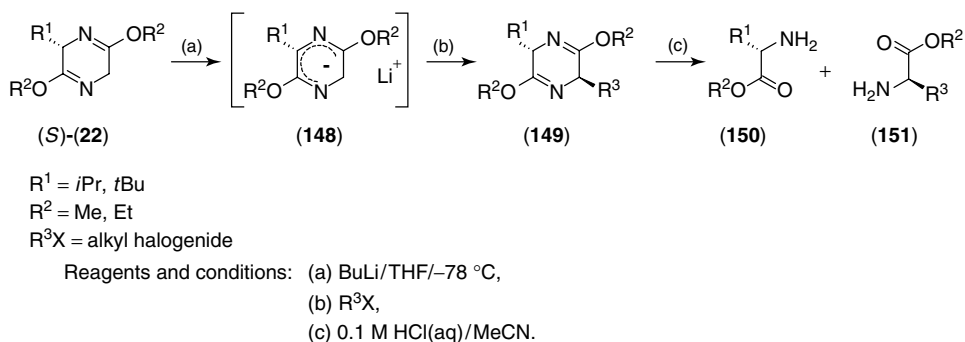
Scheme 7.64

substituent of the piperazine ring, affording *trans*-alkylated bislactim ether **149** in high diastereomeric excess, which can be hydrolyzed to the mixture of L-valine or *tert*-L-leucine ester **150** and the target enantiomerically pure  $\alpha$ -amino acid **151** [51, 97–113].

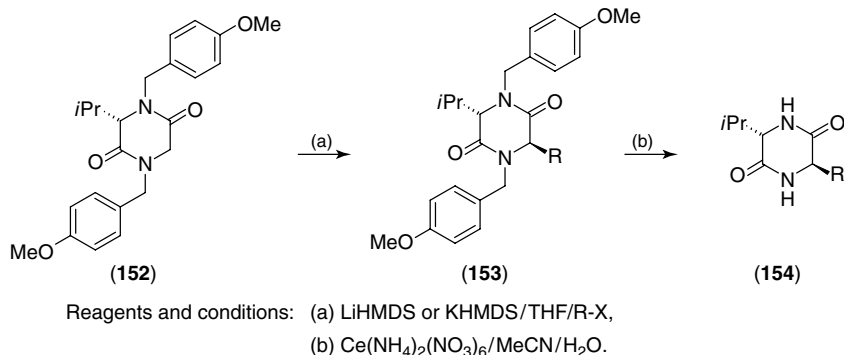
*N,N*-Bis(*p*-methoxybenzyl)piperazinedione derivative **152** was developed and used as chiral auxiliary for synthesis of enantiomerically pure amino acids. The methoxybenzyl derivative has the advantage over the dilactim ether Schöllkopf chiral auxiliaries in that it is crystalline and therefore easier to handle, and the *p*-methoxybenzyl (PMB) group can be removed under mild conditions. Thus, alkylation of the piperazine core with alkyl halides via the lithium or potassium enolate **152** afforded **153** with high diastereoselectivities, which could be deprotected to **154** [114–117].

Besides Schöllkopf chiral auxiliaries **22** and PMB derivative **152**, other piperazine precursors, such as monolactim ether **63** or piperazinones **155**, with a chiral *N*-substituent, can also be stereoselectively alkylated in essentially the same way [118–126].

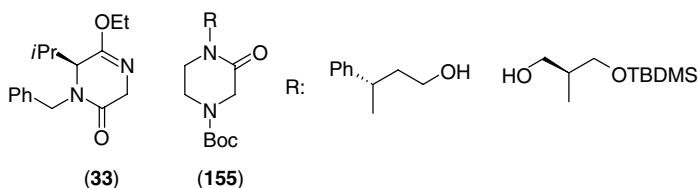
It is not necessary to use a strong base for alkylation of the piperazine ring in all cases. Mild phase transfer catalysis (PTC) conditions in the presence of a weak base have been successfully employed for the diastereoselective alkylation



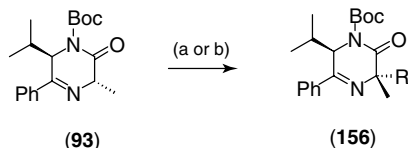
Scheme 7.65



Scheme 7.66



Scheme 7.67



R = allyl, propargyl, Bn, EtCOOCH<sub>2</sub>

Reagents and conditions: (a) R-X/K<sub>2</sub>CO<sub>3</sub>/Bu<sub>4</sub>NBr/MeCN or CH<sub>2</sub>Cl<sub>2</sub>/rt (75–86%, >94% de)  
(b) Allyl carbonates/Pd(OAc)<sub>2</sub>/PPh<sub>3</sub>/THF (75–85%, >96% de).

Scheme 7.68

of piperazinones **93** with activated halides, affording alkylated products **156**. Pd-catalyzed allylation of the same substrate was also performed by reacting **93** with allyl carbonates in the presence of Pd(OAc)<sub>2</sub> and PPh<sub>3</sub> [74, 75].

**Reaction of the Piperazine Ring with Electrophiles Different from Alkyl Halides** Not only alkyl halides but also other electrophiles, such as aldehydes, ketones, epoxides [127–129], and acyl halogenides [130], can react with enolate anions **148** to afford the corresponding alcohol.

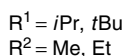
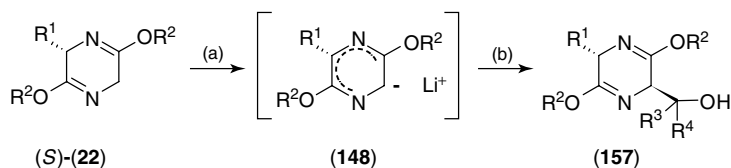
Further possibilities include Michael conjugate addition of **148** to  $\alpha,\beta$ -unsaturated esters [131–134], oxo compounds [135], or nitro compounds [136, 137] to result in the corresponding substituted piperazines. Even stereoselective arylation

of the piperazine ring is possible by the reaction of lithium enolates **182** with arene-Mn(CO)<sub>3</sub> cations [138–140].

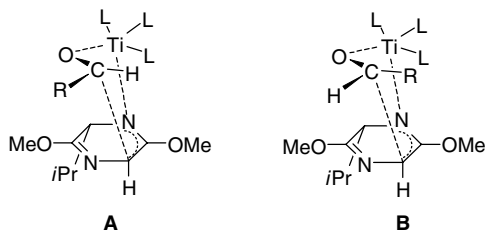
When aldehydes are reacted with **148** as such, the diastereoselectivity with regard to the heterocyclic carbon is high, whereas formation of the second chiral center at the secondary carbon in **157** ( $R^4 = H$ ) proceeds with low stereoselectivity [141–145]. However, replacement of the lithium ion in complex **148** with another metal complex (trisdimethylaminotitanium group is used in most cases) leads to a strong increase in stereoselectivity as regards the formation of the alcoholic moiety. The predominant formation of one diastereomer can be rationalized on the basis of the two six-membered pericyclic transition states **A** and **B**. Transition state **A** is lower in energy because of the quasi-diaxial repulsion between the R moiety, the methoxy group and the ligands on the metal in transition state **B** [146–149].

**Reaction of the Piperazine Ring with Nucleophiles** As revealed by the previous examples, the Schöllkopf chiral auxiliary itself serves as a nucleophilic synthon, and therefore it can be attacked by electrophiles. Its chloro derivative **158**, however, has been used as an electrophilic synthon, and the chloride in **158** could be stereoselectively replaced by malonate anions as nucleophiles, furnishing the product **159** [150].

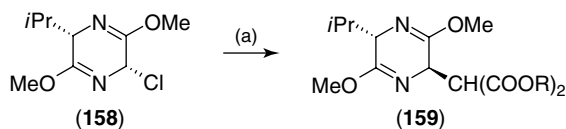
Another example of diastereoselective nucleophilic reactions on the piperazine ring is the reaction of organomagnesium or organocadmium reagents with cyclic acyl imines **161** *in situ* generated from the corresponding acetates **160**, resulting in **162** as the major and **163** as the minor diastereomer [61].



Reagents and conditions: (a) BuLi/THF/−78 °C,  
 (b)  $R^3-COR^4$  or 1. Cl(TiNMe<sub>2</sub>)<sub>3</sub>, 2.  $R^3-COR^4$ .



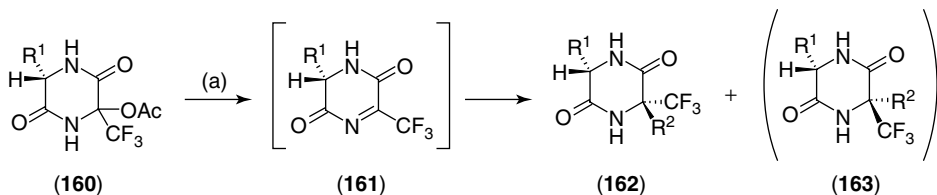
Scheme 7.69



R = Me, *i*Pr, *t*Bu

Reagents and conditions: (a) NaHC(COOR)<sub>2</sub>/THF/18-crown-6 (65%, dr 25:1 to 60:1).

Scheme 7.70

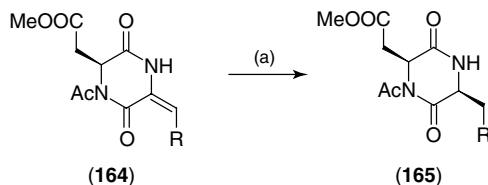


R<sup>1</sup> = Me, *i*Pr, *i*Bu, Bzl

R<sup>2</sup> = Me, Bz,

Reagents and conditions: (a) R<sup>2</sup>MgX/THF or R<sup>2</sup><sub>2</sub>Cd/THF (40–62%, de 54–99%).

Scheme 7.71



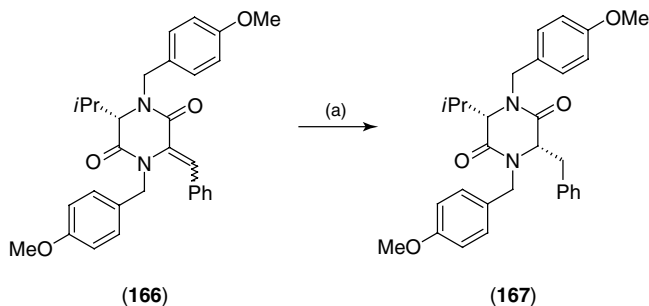
Reagents and conditions: (a) H<sub>2</sub>/Pd–C (44–97%, >97% de).

Scheme 7.72

**Asymmetric Hydrogenations** Dehydropiperazines **164** could be stereoselectively hydrogenated by using Pd/C as the catalyst giving the *cis* saturated product **165** with high diastereoselectivity [151].

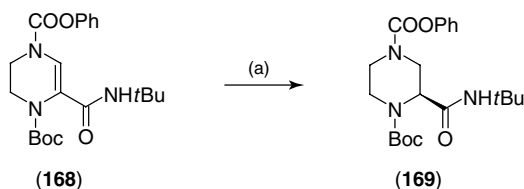
The highly diastereoselective conjugate reduction of benzylidene DKPs **166** by treatment with SmI<sub>2</sub> in THF and subsequent addition of deoxygenated water led to the *cis* 3,6-disubstituted derivative **167** on starting from either the *E* or the *Z* stereoisomer. Dideutero derivatives could also be synthesized using D<sub>2</sub>O instead of H<sub>2</sub>O [152, 153].

Tetrahydropyrazinecarboxamide **168** was reduced to the corresponding piperazine derivative **169** with moderate stereoselectivity (57% ee) by the application of rhodium catalysis using ferrocene-based phosphine ligand with planar chirality [154].



Reagents and conditions: (a)  $\text{SmI}_2/\text{THF}/\text{H}_2\text{O}$  (89–93%, 95–96% de).

Scheme 7.73



Reagents and conditions: (a)  $[\text{Rh}(\text{nbd})_2]\text{PF}_6/(\text{S},\text{S})\text{-EtTRAP-H}/\text{H}_2/\text{Cl}(\text{CH}_2)_2\text{Cl}$  (92%, 57% ee).

nbd: norbornadiene

(*S,S*)-EtTRAP-H: (*S,S*)-2,2'-bis[(diethylphosphino)methyl]-1,1'-biferrocene.

Scheme 7.74

#### 7.1.4

#### Oxadiazines

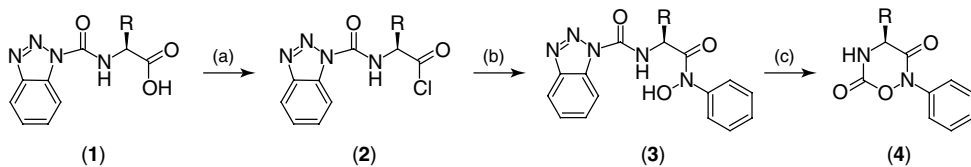
Asymmetric syntheses of oxadiazines have been far less explored than those of other rings discussed in the previous sections. The methods will be classified according to the type of the oxadiazine ring: 1,2,5-oxadiazines and 1,3,4-oxadiazines.

##### 7.1.4.1 1,2,5-Oxadiazines

1,2,5-Oxadiazines **4** were prepared from *N*-(benzotriazolylcarbonyl)-L-alanine or phenylalanine **1**, which was converted to the corresponding acyl chloride **2**. Its reaction with *N*-phenylhydroxylamine gave hydroxamic acid **3**, which readily underwent cyclization under basic conditions [155].

##### 7.1.4.2 1,3,4-Oxadiazines

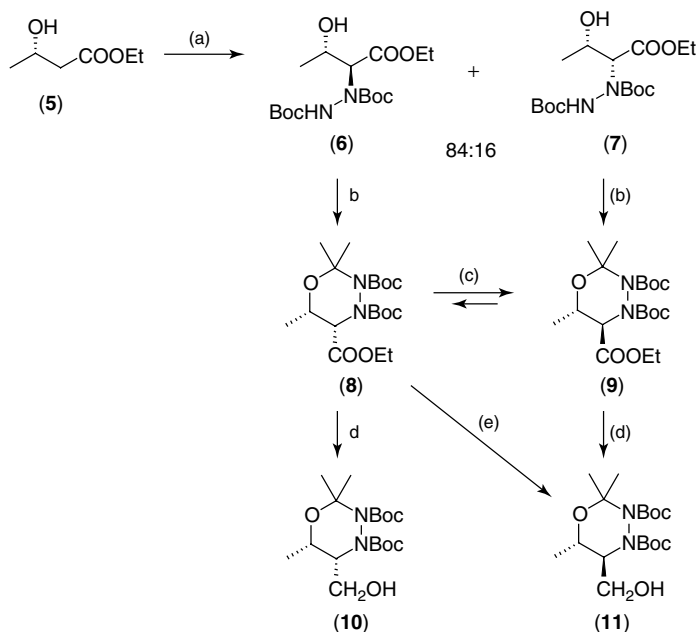
Synthesis of 1,3,4-oxadiazines **8** and **9** started from ethyl (*S*)-3-hydroxybutyrate (**5**). Diastereoselective amination with di-*tert*-butylazodicarboxylate gave an 84:16 mixture of hydrazino ester epimers **6** and **7**. Treatment of **6** with 2,2-dimethoxypropane afforded oxadiazine **8**, which underwent base-catalyzed equilibration to give the more stable *trans* product **9** (*trans/cis* ratio = 98:2). The latter compound



R = Me, Bn

Reagents and conditions: (a)  $\text{SOCl}_2$ , (b)  $\text{PhNHOH}/N\text{-methylmorpholine}/\text{toluene}$  (15–31%),  
(c)  $\text{Na}_2\text{CO}_3/\text{H}_2\text{O}/\text{acetone}$  (28%).

Scheme 7.75



Reagents and conditions: (a)  $\text{LDA}/\text{CbzNNCBz}$ , (b)  $(\text{MeO})_2\text{CMe}_2/p\text{TsOH}/\text{benzene}/\text{rt}/\text{rfd}$  (75% for **8**, 61% for **9**), (c)  $\text{NaH}/\text{EtOH}/\text{THF}/\text{rt}/1\text{d}$  (78%),  
(d)  $\text{Ca}(\text{BH}_4)_2$  (from 3.5 equiv  $\text{CaCl}_2$  and 6 equiv  $\text{NaBH}_4$ ),  $\text{EtOH}/\text{THF}$  (91–92%), (e)  $\text{Ca}(\text{BH}_4)_2$  (from 3 equiv  $\text{CaCl}_2$  and 6.5 equiv  $\text{NaBH}_4$ )  $\text{NaOEt}/\text{EtOH}/\text{THF}$  (86%).

Scheme 7.76

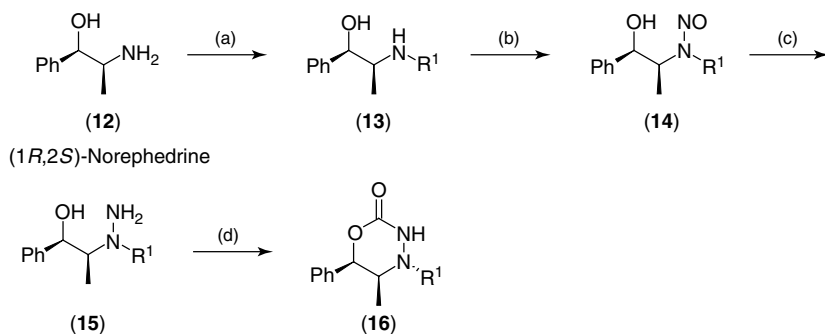
could also be obtained from the *syn* hydrazino derivative **7**. The esters **8** and **9** were reduced to the corresponding hydroxymethyl derivative **10** and **11** by  $\text{Ca}(\text{BH}_4)_2$  *in situ* formed from  $\text{CaCl}_2$  and  $\text{NaBH}_4$ . However, the *cis* isomer was sensitive to the conditions of the reduction: when  $\text{CaCl}_2$  was used in a slight excess compared to  $\text{NaBH}_4$ , no epimerization took place; on the contrary, employing  $\text{NaBH}_4$  in excess resulted in nearly complete conversion to the more stable *trans* alcohol **11** [156, 157].

Another method was applied by Hitchcock *et al.* for the synthesis of the 1,3,4-oxadiazine ring. They synthesized 3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **16** starting from enantiomerically pure natural amino alcohols such as ephedrine, norephedrine or their stereoisomers. Introduction of alkyl moiety to the primary amino group in **12** could be carried out by condensation with a suitable oxo compound under reductive conditions. Subsequent treatment of **13** with  $\text{NaNO}_2/\text{HCl}$  gave *N*-nitrosamines **14**, which were reduced to  $\beta$ -hydrazinoalcohols **15**. Cyclization of **15** could be performed either by using 1,1'-carbonyldiimidazole or diethyl carbonate to afford oxadiazinones **16** (Scheme 7.77) [158–162].

Oxadiazines **17** and **18** could also be prepared principally by the same way starting from the corresponding amino alcohol [162–164].

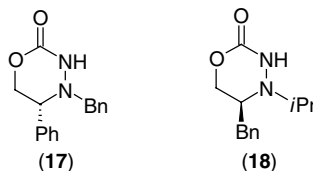
3,4,5,6-Tetrahydro-2*H*-1,3,4-oxadiazin-2-ones **36** were used as chiral auxiliaries. Asymmetric aldol reactions of acylated oxadiazinone **19** with various aldehydes via titanium enolate afforded adducts **20**. When aldehydes without an  $\alpha$ -hydrogen were employed, the products were obtained in high yields and diastereoselectivities; in contrast to this finding, by employment of aldehydes bearing an  $\alpha$ -hydrogen, moderate diastereoselectivities were achieved.

The observed stereoselectivity could be explained by the conformation of the oxadiazinone ring, in which the *N*-4 substituent blocks the *si* face of the *N*-3 acyl substituent (see scheme) [165–169].

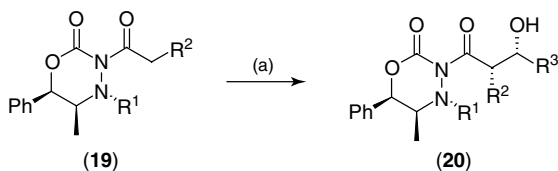


$\text{R}^1 = i\text{Pr}, n\text{Bn}, \text{Me}$   
 $\text{R}^2 = \text{Me}, \text{Bn}, \text{bornyl}$

Reagents and conditions: (a)  $\text{Me}_2\text{CO}$  or  $\text{PhCHO}/\text{NaBH}_4$ , (b)  $\text{NaNO}_2/\text{HCl}/\text{THF}$  (95–97%), (c)  $\text{LiAlH}_4/\text{THF}$ , (d)  $(\text{EtO})_2\text{CO}/\text{LiH}/\text{hexane}$  or  $\text{CDI}/p\text{TsOH}$  (74%), (e)  $\text{LiH}/\text{RCOCl}/\text{CH}_2\text{Cl}_2$  (43–95%).



Scheme 7.77

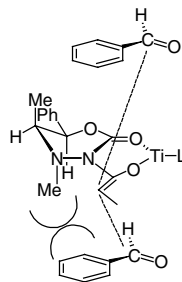


R<sup>1</sup> = Me, *i*Pr, bornyl

R<sup>2</sup> = Me, PhSCH<sub>2</sub>, MeO, BnO, PhO

R<sup>3</sup> = aryl, *t*Bu, alkyl

Reagents and conditions: (a) 1. R<sup>3</sup>CHO/THF, 2. Et<sub>3</sub>N, 3. TiCl<sub>4</sub> (62–97%, dr 75:25 to 99:1 for aldehyde without  $\alpha$ -hydrogen, 8:1 to 38:1 with  $\alpha$ -hydrogen).



Scheme 7.78

### 7.1.5

#### Morpholines

Morpholine derivatives with defined configuration of the substituents can be obtained either by cyclization of enantiomerically pure starting material or by asymmetric transformation of the morpholine ring.

A review appeared in *Synthesis* in 2004 summarizing syntheses of C-substituted morpholine derivatives. It classifies the methods according to the type of starting material or reaction type; thus syntheses from amino alcohols, epoxides, olefins, and carboxylic acid derivatives and via organometallic reactions are described [170].

In the first part of this section, we follow a classification of the ring closures according to the method of cyclization: lactone or lactam formation, imine bond formation, nucleophilic substitution, conjugate addition, and by the involvement of organometallics. In the second part, asymmetric alkylations, arylations, radical additions, and hydrogenations on the morpholine ring are discussed.

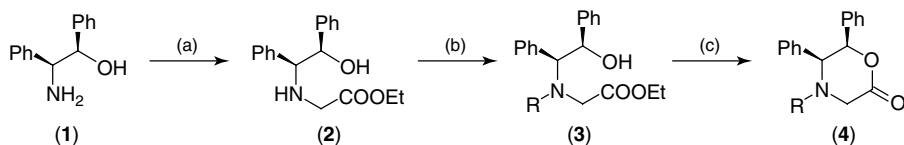
##### 7.1.5.1 Formation of the Morpholine Ring

**Ring Closure by Lactone or Lactam Formation** A frequent route to the synthesis of enantiomerically pure morpholinone derivatives is the cyclization of a suitably substituted enantiomerically pure *N*-(2-hydroxyethyl)- $\alpha$ -amino acid or ester by lactone formation. Thus, (1*R*,2*S*)-2-amino-1,2-diphenyl ethanol (**1**) was N-alkylated with ethyl bromoacetate in the presence of a weak base to afford **2**; subsequent N-protection and acidic cyclization gave 4-protected-5,6-diphenylmorpholin-2-ones **4** via intermediates **3** [171].

In the same pathway, differently substituted morpholinone derivatives were also synthesized [172–176].

Similar to the previous example, the hydroxy ester suitable for lactonization was prepared by N-alkylation of an amino alcohol; diastereoselective coupling between racemic  $\alpha$ -halo acids **5** and *N*-benzylethanolamine (**6**) was performed in the presence of Bu<sub>4</sub>NI, and **7** obtained with high diastereoselectivity was then cyclized to oxazinones **8** upon treatment with *p*TsOH [177].

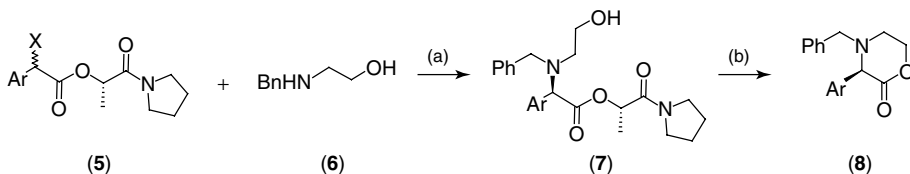




R = Boc, Cbz

Reagents and conditions: (a)  $\text{BrCH}_2\text{COOEt}/\text{Et}_3\text{N}/\text{THF}$ , (b)  $\text{Boc}_2\text{O}/\text{toluene}$  or  $\text{CbzCl}/\text{CH}_2\text{Cl}_2/\text{NaHCO}_3$  (aq), (c)  $p\text{TsOH}/\text{toluene}$  (75–86% overall).

Scheme 7.79

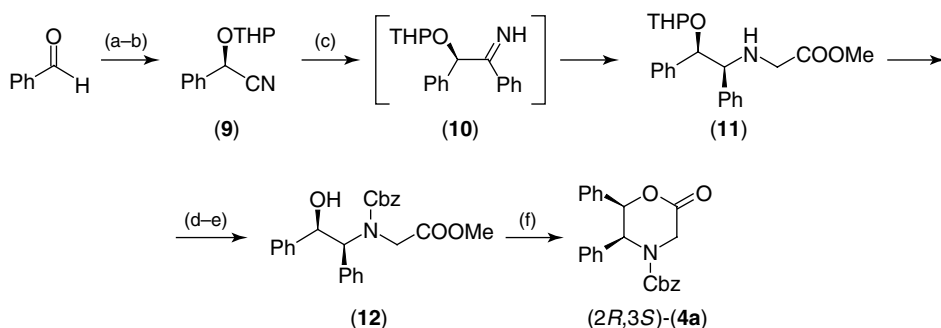


Reagents and conditions: (a)  $\text{Et}_3\text{N}/\text{THF}/\text{Bu}_4\text{NI}$  (84–90%, 76–96% de), (b)  $\text{toluene}/p\text{TsOH}$  (82%, 86–91% ee).

Scheme 7.80

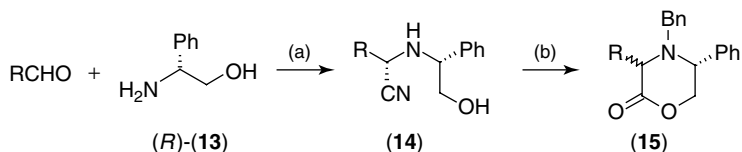
Diphenylmorpholine (2*R*,3*S*)-**4a** was prepared in enantiomerically pure form in six steps starting from benzaldehyde. Enzymatic stereoselective HCN addition to the aldehyde was followed by O-protection to **9**, which was then converted to **11** via a one-pot Grignard addition–transamidation–reduction sequence. The reduction proceeded with complete diastereoselectivity to **11**, which upon O-deprotection gave **12**. Subsequent N-protection and acidic cyclization resulted in morpholine (2*R*,3*S*)-**4a** [178].

Asymmetric Strecker reaction of various aldehydes and (*R*)-2-phenylglycinol (**13**) gave nitriles **14**, which were esterified with methanolic HCl. The esters were cyclized



Reagents and conditions: (a)  $\text{HCN}/\text{oxynitrilase}$  (99% ee), (b)  $p\text{TsOH}/\text{Et}_2\text{O}/\text{dihydropyran}$ , (c) 1.  $\text{PhMgBr}/\text{Et}_2\text{O}$ , 2.  $\text{MeOH}$ , 3.  $\text{NH}_2\text{CH}_2\text{COOMe}$ , 4.  $\text{NaBH}_4$ , (d)  $p\text{TsOH}/\text{MeOH}$ , (e)  $\text{CbzCl}$ , (f)  $p\text{TsOH}/\text{cyclohexane}$  (48% overall).

Scheme 7.81



R = Me, Bn, *n*Pr, BnO(CH<sub>2</sub>)<sub>2</sub>

Reagents and conditions: (a) NaCN/NH<sub>4</sub>Cl/MeOH/H<sub>2</sub>O, (b) 1. HCl/MeOH, 2. toluene/*p*TsOH, 3. BnBr/K<sub>2</sub>CO<sub>3</sub>/DMF (overall: 33–48%, 66–80% de).

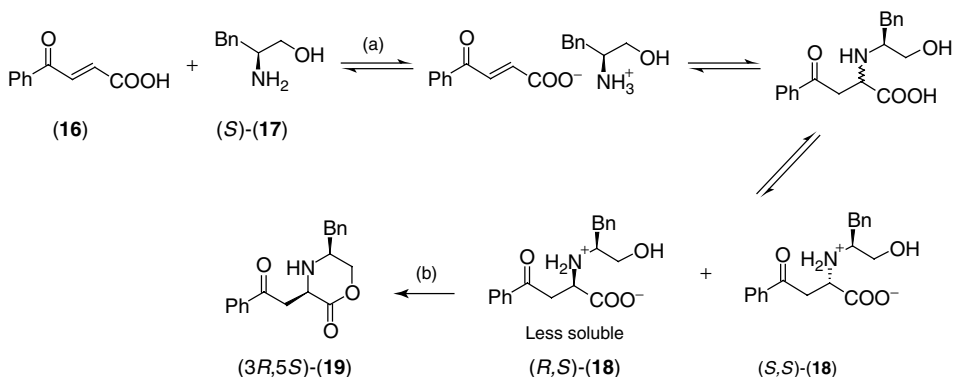
Scheme 7.82

in the presence of *p*TsOH, and the intermediates obtained were N-benzylated to compounds **15**. Good diastereoselectivities were achieved [179].

The 3*R*,5*S*-disubstituted morpholinone **19** was elegantly obtained in the following pathway. A highly stereoselective (dr: 95:5) conjugate addition of amino alcohol (*S*)-**17** to unsaturated oxocarboxylic acid **16** in combination with crystallization-induced dynamic resolution (CIDR) provided the hydroxyethylamino carboxylic acid derivative (*R,S*)-**18** in high diastereoselectivity, which, by lactonization, led to (3*R*,5*S*)-**19**. In the CIDR process, the solvent plays an important role: the solubility of the arising amino acid should be as low as possible, but high enough to permit the equilibration processes [180].

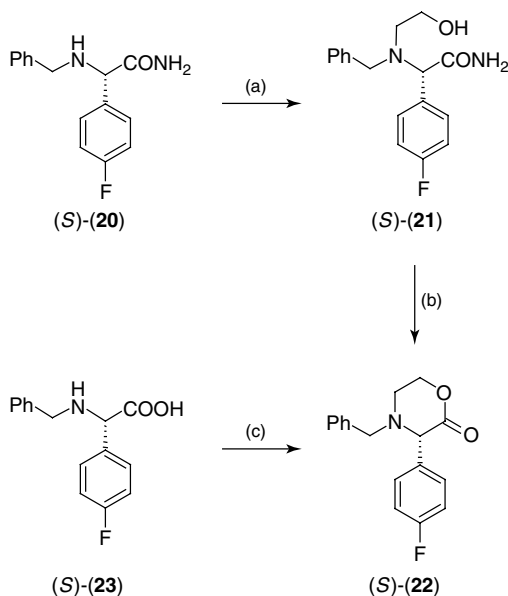
Lactone formation for synthesis of compound (*S*)-**22** could be carried out either by cyclization between a hydroxy function and a carboxylic amide moiety in (*S*)-**21** derived from amino acid amide (*S*)-**20** or by reacting amino acid (*S*)-**23** with 1,2-dibromoethane [181].

Reacting ephedrine **24** with  $\alpha$ -oxocarboxylic acid chlorides results in lactol formation, giving compounds **25** after N-acylation [182].



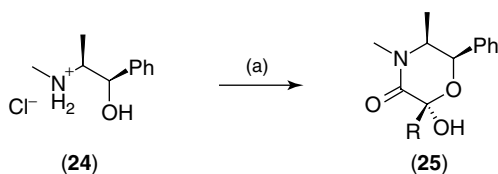
Reagents and conditions: (a) EtOH or CH<sub>2</sub>Cl<sub>2</sub>/25–30 °C/7d (for (*R,S*)-**18**: 81%, dr 95:5), (b) THF/H<sub>2</sub>SO<sub>4</sub>/rt (60%).

Scheme 7.83



Reagents and conditions: (a)  $\text{BrCH}_2\text{CH}_2\text{OH}/i\text{Pr}_2\text{NEt}/\text{DMF}$  (75%),  
 (b)  $\text{AcOH}/60\text{ }^\circ\text{C}$  (95%), (c)  $\text{Br}(\text{CH}_2)_2\text{Br}/i\text{Pr}_2\text{NEt}$ .

**Scheme 7.84**



$\text{R} = \text{Me, Et, } n\text{Pr, } i\text{Pr}$

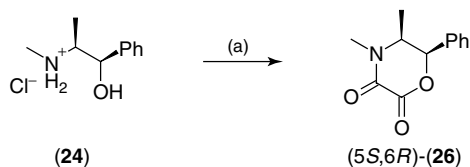
Reagents and conditions: (a)  $\text{RCOCOCi}/\text{Et}_3\text{N}/\text{DMAp}/\text{CH}_2\text{Cl}_2$   
 (65–71%).

**Scheme 7.85**

Lactone and lactam formation took place by reacting ephedrine **24** with oxalyl chloride, affording morpholine-2,3-dione (5*S*,6*R*)-**26** [183–185].

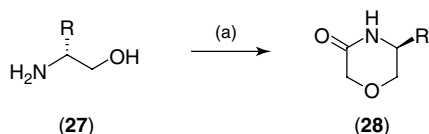
Reaction of amino alcohols with an  $\alpha$ -halo ester in the presence of weak base results in N-alkylation (see above), while treatment of amino alcohols **27** with a strong base as NaH followed by addition of ethyl chloroacetate gave O-alkylated derivative of **27**, which spontaneously cyclized to form lactam **28** [186].

Morpholine-2,5-diones can be considered as lactones and lactams in the same ring. Two different approaches could be applied for their synthesis: (i) first ester formation of the hydroxy moiety of an  $\alpha$ -hydroxy acid with an amino acid, followed by intramolecular amide formation as the ring closure step give the product or (ii) the amide formed in the first step is cyclized via lactonization.



Reagents and conditions: (a)  $(\text{COCl})_2/\text{Et}_3\text{N}/\text{DMAP}/\text{CH}_2\text{Cl}_2$  (65–71%).

Scheme 7.86



R = Me, Bn, *i*Bu, *t*Bu, *s*Bu

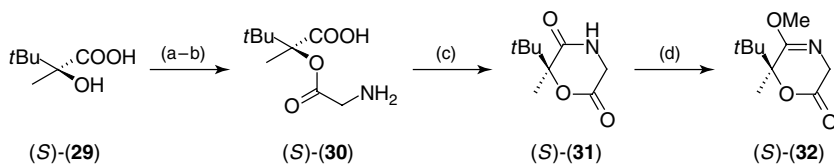
Reagents and conditions: (a)  $\text{NaH}/\text{ClCH}_2\text{COOEt}/\text{THF}$  (69–88%).

Scheme 7.87

According to the first approach, synthesis of (*S*)-**32** started from hydroxy acid (*S*)-**29**, which was coupled with 1,1'-carbonyldiimidazole (CDI)-activated Cbz-glycine yielding amino acid (*S*)-**30** after deprotection. Cyclization of (*S*)-**30** took place upon treatment with Mukaiyama reagent. The lactam (*S*)-**31** could be transformed to lactim (*S*)-**32** using  $\text{Me}_3\text{OBF}_4$  [187].

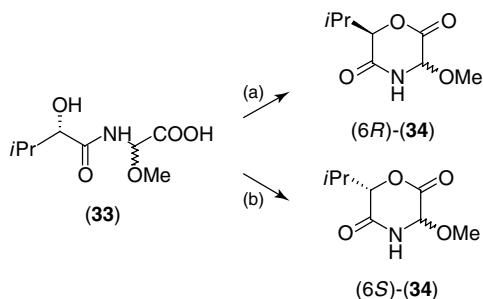
Employing the second approach, depending on the reaction conditions, two different stereoisomeric products were formed starting from the acid **33**. By treatment with diethyl azodicarboxylate and triphenyl phosphine, intramolecular Mitsunobu reaction with inversion of the configuration led to (*6R*)-**34**, while heating **33** under reduced pressure resulted in (*6S*)-**34** via spontaneous cyclization with retention [170–188].

The *N*-benzyl-protected amino alcohol **6** was cyclized with glyoxylic acid (**35**), then the product **36** activated with  $\text{TiF}_2\text{O}$  and reacted with the alcohol **37** followed by crystallization driven epimerization, affording (*2R*,1'*R*)-**38** in 99% diastereomeric excess [170, 189].



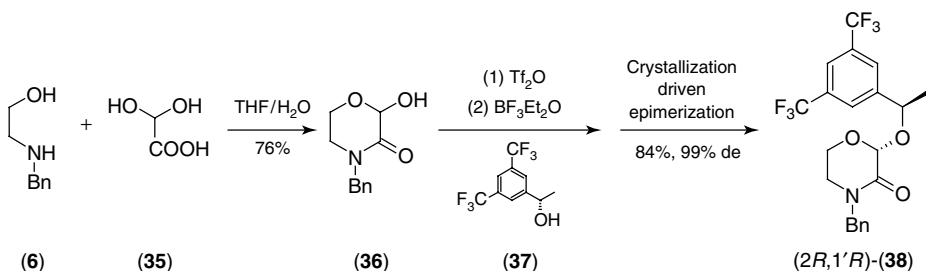
Reagents and conditions: (a) Cbz-glycine/CDI/THF (86%), (b)  $\text{H}_2/\text{Pd}-\text{C}/\text{EtOH}$  (96%), (c) 2-chloro-1-methylpyridinium iodide/*i*Pr<sub>2</sub>NEt/ $\text{CH}_2\text{Cl}_2$  (84%), (d)  $\text{Me}_3\text{OBF}_4/\text{CH}_2\text{Cl}_2$  (89%).

Scheme 7.88



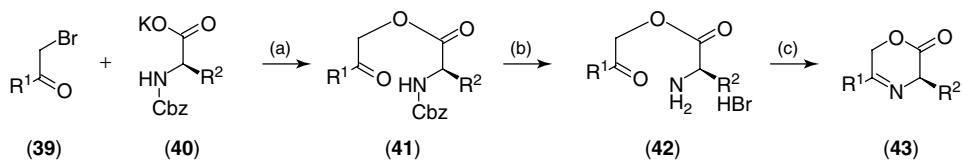
Reagents and conditions: (a) DEAD/ $\text{PPh}_3$  (30%),  
(b) 65 °C/0.2 bar (95%).

Scheme 7.89



Scheme 7.90

**Ring Closure via Imine/Enamine Bond Formation** Intramolecular condensation of an oxo group with an amino moiety is also a suitable way of morpholine ring formation. Thus, for the synthesis of 43, ketones 39 halogenated at  $\alpha$ -position and potassium salts 40 of *N*-protected  $\alpha$ -amino acids were condensed to give esters 41, which were then deprotected to 42. Cyclization to morpholinones 43 could be performed in acetate buffer to avoid pH decrease during the reaction, which would cause hydrolysis and slow down the cyclization [190].



$\text{R}^1 = \text{aryl}$ ,  $\text{R}^2 = \text{Me}$ , Bz, *i*Pr

Reagents and conditions: (a) DMF/rt (74–100%), (b) HBr/AcOH/rt (80–99%),  
(c) 0.2 M acetate buffer/rt (65–90%).

Scheme 7.91

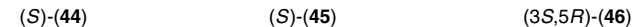
above.

the product [194].

methyl 3-(chlorocarbonyl)propanoate (47) by addition of diazomethane followed by

of amino alcohol (2*S*,1'*S*)-**51** with glyoxal [196].

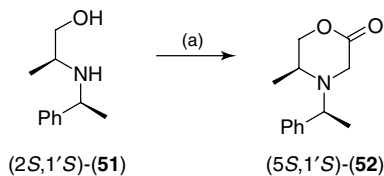
intermediate **55**. In this reaction sequence, stereoselective formation of the new



(f)  $\text{H}_2/\text{Pd}-\text{C}/\text{EtOAc}$  (86%).

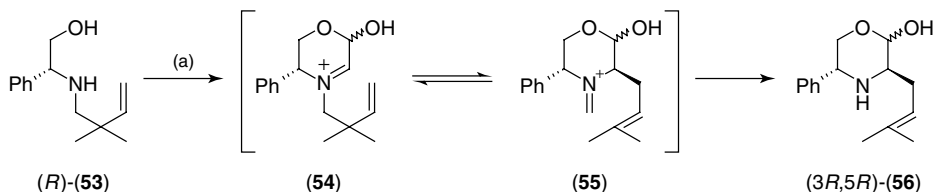


(c) 1. TFA/CH<sub>2</sub>Cl<sub>2</sub>; 2. NaCN/*i*PrOH (64% dr 18:1)



Reagents and conditions: (a) OHC–CHO/THF/rfx (86%).

Scheme 7.94



Reagents and conditions: (a) OHC–CHO/H<sub>2</sub>O (54%).

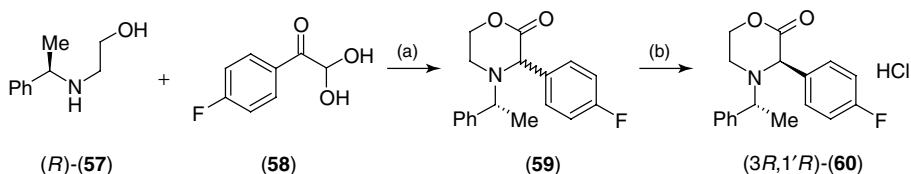
Scheme 7.95

chiral center at 3 position was observed giving exclusively the 3*R* stereoisomer [197–199].

Reaction of amino alcohol (*R*)-**57** with 4-fluorophenylglyoxal **58** yielded a mixture (1:2) of the diastereomers **59**. However, the newly formed chiral center was labile under acidic conditions, and when the diastereomeric mixture was treated with HCl in isopropyl alcohol, the 3*R* isomer crystallized preferentially and nearly all of the other diastereomer was converted into the 3*R* isomer leading to formation of (3*R*,1'*R*)-**60** in excellent yield and stereoselectivity (98% de) [170, 200].

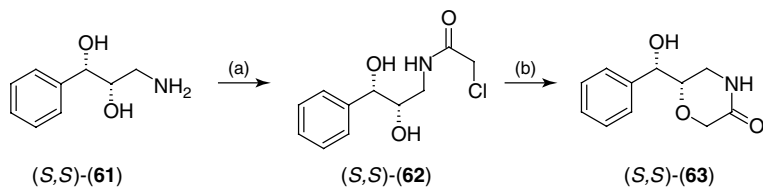
**Ring Closure via Nucleophilic Substitution with C–O Bond Formation** Intramolecular displacement of a halogen with a hydroxy group in a suitable haloacetyl aminoethanol derivative can be used for morpholine ring formation. Thus, compound (*S,S*)-**62** prepared by acylation of amino alcohol (*S,S*)-**61** with chloroacetyl chloride was treated with KO<sup>*t*</sup>Bu to give morpholinone (*S,S*)-**63** [201, 202].

Optically active 2-hydroxymethylmorpholine derivatives (*S*)-**67** and (*R*)-**69** could be prepared from precursors possessing the stereogenic center from natural origin. Namely, the protected D-mannitol derivative **64** was cleaved with sodium



Reagents and conditions: (a) AcOH, (b) HCl/*i* PrOAc (90%, 98% de).

Scheme 7.96

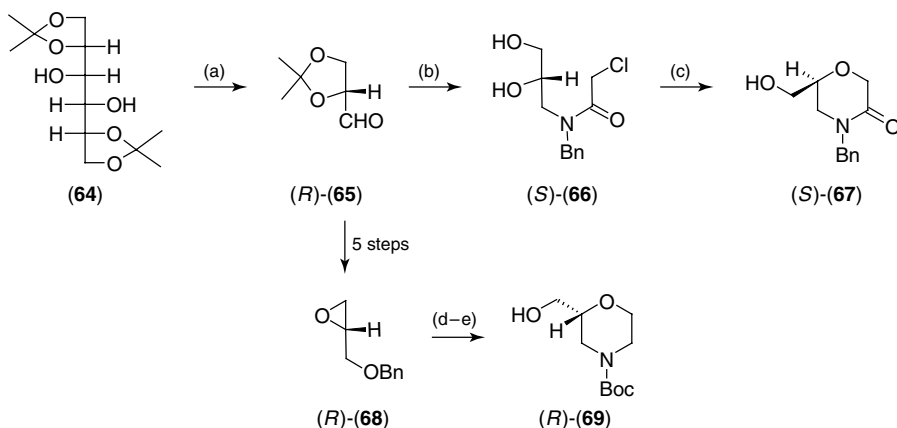


Reagents and conditions: (a)  $\text{ClCH}_2\text{COCl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$  (70%),  
 (b)  $\text{KOtBu}/\text{BuOH}$  (80%).

Scheme 7.97

metaperiodate to aldehyde (*R*)-**65**, and reductive amination with benzyl amine followed by acylation with chloroacetyl chloride and subsequent deprotection gave (*S*)-**66**, which was then cyclized to the product (*S*)-**67** with *S* configuration by treatment with  $\text{NaOEt}$ . Since the enantiomer of (*S*)-**67** could not be prepared in a stereochemically pure form by inversion of the configuration of (*S*)-**66** as the key step, another route was applied. Treatment of the epoxide (*R*)-**68** prepared from (*R*)-**65** in five steps with aminoethyl hydrogensulfate gave the cyclized product, which was then debenzylated to (*R*)-**69** [203].

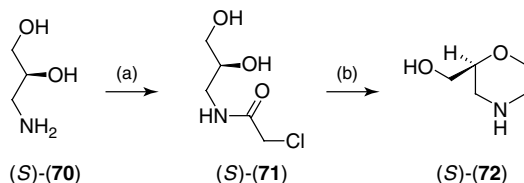
Enantiomerically pure starting material, (*S*)-3-amino-1,2-propanediol ((*S*)-**70**), was also used for the preparation of (*S*)-2-hydroxymethylmorpholine ((*S*)-**72**) as a key intermediate for the synthesis of the selective norepinephrine inhibitor reboxetine. After *N*-acylation of (*S*)-**70** with chloroacetyl chloride, (*S*)-**71** could be cyclized to morpholine (*S*)-**72** with  $\text{KOtBu}$  [204].



Reagents and conditions: (a)  $\text{NaIO}_4/\text{H}_2\text{O}$ , (b) 1.  $\text{BnNH}_2/\text{EtOH}/\text{H}_2\text{O}/\text{Raney-Ni}/\text{H}_2$  (quant),  
 2.  $\text{ClCH}_2\text{COCl}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ , (86%), 3. 20% aq  $\text{AcOH}$  (quant),  
 (c)  $\text{NaOEt}/\text{EtOH}$  (88%), (d) 1.  $\text{H}_2\text{N}(\text{CH}_2)_2\text{OSO}_3\text{H}/\text{NaOH}/\text{H}_2\text{O}$  (62%),  
 2.  $\text{Boc}_2\text{O}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ , (88%), (e)  $\text{Pd-C}/\text{H}_2/\text{MeOH}$  (quant).

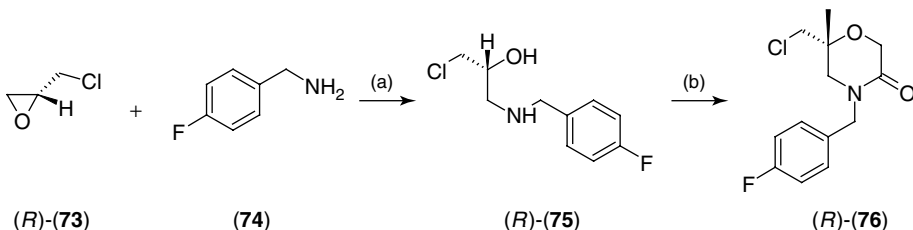
Scheme 7.98





Reagents and conditions: (a)  $\text{ClCH}_2\text{COCl}/\text{Et}_3\text{N}/\text{MeCN}/\text{MeOH}$  (94%),  
(b)  $\text{KO}^t\text{Bu}/t\text{AmOH}$  (92%).

**Scheme 7.99**

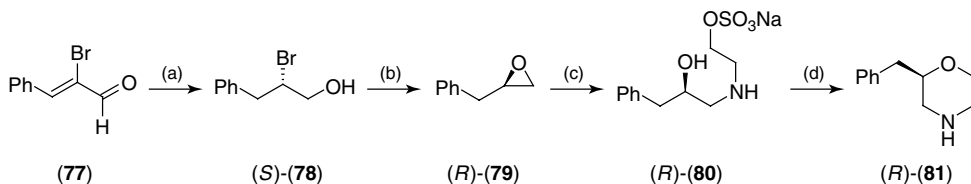


Reagents and conditions: (a) cyclohexane/rt (70%, 98% ee),  
(b)  $\text{BrCH}_2\text{COBr}/\text{NaOH}/\text{H}_2\text{O}/\text{CHCl}_3$  (86%).

**Scheme 7.100**

Synthesis of the morpholine derivative (*R*)-**76** as an intermediate for the gastro-protecting agent mosapride started from (*R*)-(-)-epichlorohydrin ((*R*)-**73**). Using hydrocarbons as cyclohexane as the solvent proved to be more efficient over other solvents in the reaction of (*R*)-**73** with 4-fluorobenzylamine (**74**) furnishing the product (*R*)-**75** in good yield and high enantiomeric purity. Reaction of (*R*)-**75** with bromoacetyl bromide in a mixture of chloroform and 30% aqueous NaOH solution resulted in the ring-closed product (*R*)-**76** without isolation of the bromoacetamide intermediate [205].

Enzymatic synthesis of enantiomerically pure morpholine (*R*)-**81** could be achieved through an epoxide intermediate, where the key step is the asymmetric reduction of the bromoaldehyde **77** to bromo alcohol (*S*)-**78** using baker's yeast.



Reagents and conditions: (a) Baker's yeast/XAD1180 resin (100%, 98.6% ee), (b)  $\text{NaOH}/\text{H}_2\text{O}$  (73%),  
(c)  $\text{H}_2\text{N}(\text{CH}_2)_2\text{OSO}_3\text{Na}/\text{NaOH}/\text{MeOH}$ , (d)  $\text{NaOH}/\text{toluene}$  (66%).

**Scheme 7.101**

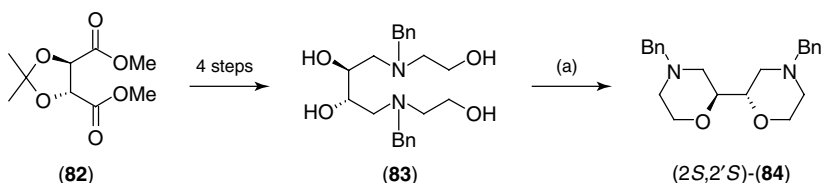
Ring opening of the epoxide (*R*)-**79** with ethanolaminesulfonate to (*R*)-**80** and subsequent basic cyclization gave (*R*)-**81** [170].

For the synthesis of *N,N'*-dibenzyl derivative of (2*S*,2'*S*)-2, 2'-bimorpholine (2*S*,2'*S*)-**84**, tetraol **83** prepared from tartaric acid derivative **82** was cyclized in a one-step procedure with NaH and *p*-toluenesulfonyl imidazole [206].

*trans*-2,5-Disubstituted morpholine derivative (2*S*,5*R*)-**88** was prepared starting from enantiomerically pure epoxide (*S*)-**85** and D-alaninol (*R*)-**86** via diol **87** applying the same cyclization method. Thus, refluxing (*S*)-**85** and (*R*)-**86** in *n*-propanol and subsequent N-tosylation yielded selectively diol **87**, which was then cyclized via deprotonation with NaH in the presence of *p*-toluenesulfonyl imidazole. Removal of the tosyl group with sodium in ethanolic ammonia provided (2*S*,5*R*)-**88** in pure form [207].

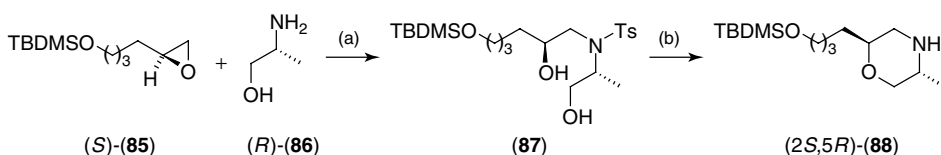
However, adaptation of the method bearing larger substituents was not unambiguous. When attempting the same reaction sequence for synthesis of analogous morpholine derivatives with larger 5-substituents (e.g. phenyl and benzyl), ring opening proceeded smoothly, but instead of selective N-tosylation, O-tosylation occurred as a result of sterical hindrance. For the preparation of the N-tosylated diol (analog of **87**), first, transient protection of hydroxy groups was necessary with trimethylsilyl groups. Ring closure of the phenyl analog of diol **87** was also unsuccessful using the same procedure (NaH/TsIm) as used for **87**, but O-tosylation and subsequent treatment with K<sub>2</sub>CO<sub>3</sub> in *t*BuOH resulted in the cyclized product [207].

An enantioselective route to reboxetine analog (*S,S*)-**94** with *S,S* configuration was described, where the key step was the Sharpless asymmetric epoxidation of the cinnamyl alcohol derivative **89** to epoxide (*R,R*)-**90** in 85% ee. The stereochemical outcome was highly dependent on the oxidating agent: the best enantiomeric excess was achieved by using cumene hydroperoxide. The (*R,R*) enantiomer of the product



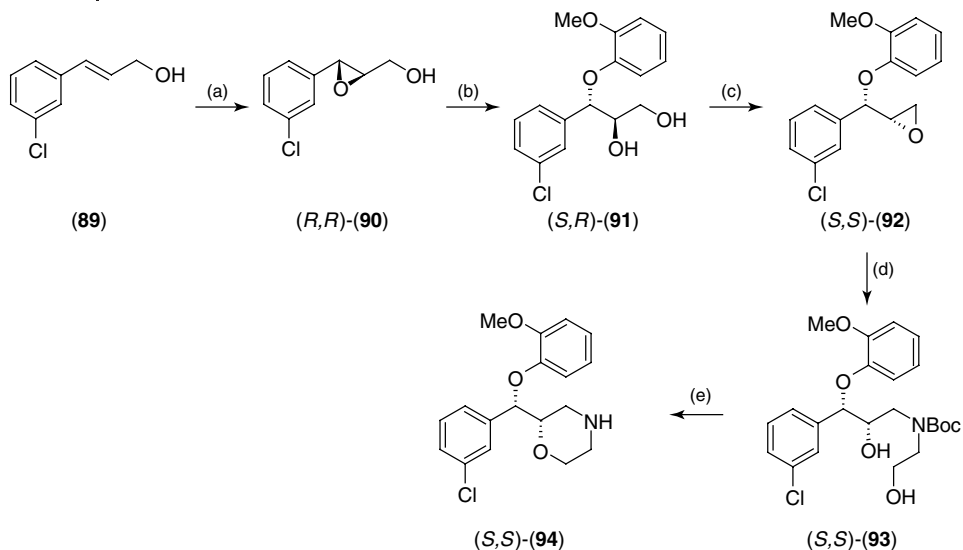
Reagents and conditions: (a) NaH/THF/TsIm (82%, 50% overall, 99% ee).

Scheme 7.102



Reagents and conditions: (a) 1. *n*PrOH/rfx (99%), 2. TsCl/Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> (77%),  
(b) 1. NaH/THF/TsIm (99%), 2. Na/NH<sub>3</sub>/EtOH (100%).

Scheme 7.103



Reagents and conditions: (a)  $\text{Ti}(\text{O}i\text{Pr})_4/\text{cumene hydroperoxide}/\text{D-DET}/\text{CH}_2\text{Cl}_2/\text{mol. sieves}$  (72%, 85% ee), (b) guaiacol/ $\text{NaOH}/\text{CH}_2\text{Cl}_2$ , (c) 1.  $\text{TMSCl}/\text{Et}_3\text{N}/\text{EtOAc}$ , 2.  $\text{MsCl}/\text{Et}_3\text{N}/\text{EtOAc}$ , 3.  $1\text{N HCl}$ , 4.  $\text{NaOH}/\text{toluene}/\text{MeBu}_3\text{NCl}$  (60%), (d) 1. ethanolamine/ $i\text{PrOH}$ , 2.  $\text{Boc}_2\text{O}/\text{CH}_2\text{Cl}_2$  (83%), (e) 1.  $\text{NaH}/\text{TsIm}/\text{THF}$  (61%), 2.  $\text{TFA}/\text{CH}_2\text{Cl}_2$  (93%).

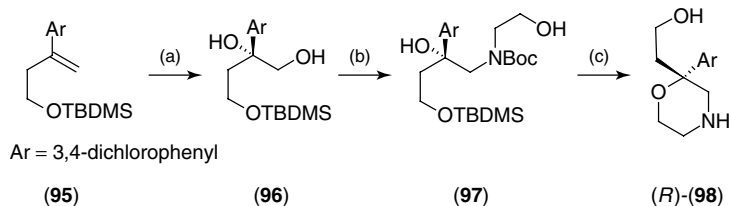
#### Scheme 7.104

could be obtained using *L*-diethyl tartrate (DET) instead of *D*-DET as the additive. Ring opening of *(R,R)*-90 with guaiacol gave diol *(S,R)*-91, which was then transformed to epoxide *(S,S)*-92 in four steps. Reaction of *(S,S)*-92 with ethanolamine, and the subsequent N-protection and cyclization of *(S,S)*-93 with tosylimidazol gave *(S,S)*-94 [208].

Starting from olefin 95, Sharpless dihydroxylation was performed affording diol 96 in 98% ee. Selective tosylation on the primary hydroxy group, followed by nucleophilic substitution with ethanolamine and N-protection gave compound 97, which was cyclized under Mitsunobu conditions, and then deprotected to morpholine derivative *(R)*-98 [170, 209].

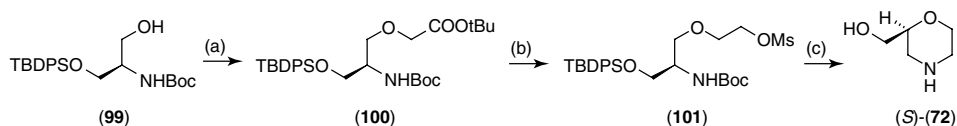
**Ring Closure via Nucleophilic Substitution with C–N Bond Formation** Another pathway for the synthesis of *(S)*-2-hydroxymethylmorpholine (72) from enantiomerically pure starting material involved the alkylation of the protected amino alcohol 99 derived from *L*-serine with *tert*-butyl bromoacetate to ester 100, which was then reduced in two stages to the corresponding alcohol. Subsequent mesylation to 101 and base-mediated cyclization followed by deprotection gave *(S)*-72 [210].

Using *(R)*-1-benzylglycerol (*(R)*-102), *S*- and *R*-hydroxymethylmorpholine derivatives *(S)*-105 and *(R)*-108, respectively, could be prepared selectively via the key intermediate 103 by varying the removal of the applied protecting groups. Thus, the



Reagents and conditions: (a) AD-mix- $\beta$ /tBuOH/H<sub>2</sub>O (94%, 98% ee),  
 (b) 1. TsCl/pyridine, 2. ethanolamine/LiClO<sub>4</sub>/MeCN,  
 3. Boc<sub>2</sub>O/Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> (86%), (c) 1. DEAD/PPh<sub>3</sub>/toluene,  
 2. 4 N HCl/dioxane, 3. 5% NaOH.

Scheme 7.105



Reagents and conditions: (a) BrCH<sub>2</sub>COOt-Bu/aq NaOH/toluene/Bu<sub>4</sub>NI (87%), (b) 1. DIBAL-H/CH<sub>2</sub>Cl<sub>2</sub>,  
 2. LiBH<sub>4</sub>/Et<sub>2</sub>O (85%), 3. MsCl/Et<sub>3</sub>N/CH<sub>2</sub>Cl<sub>2</sub> (93%),  
 (c) 1. TFA/CH<sub>2</sub>Cl<sub>2</sub>, 2. DIEA/MeOH, 3. *n*Bu<sub>4</sub>NF/THF (87%).

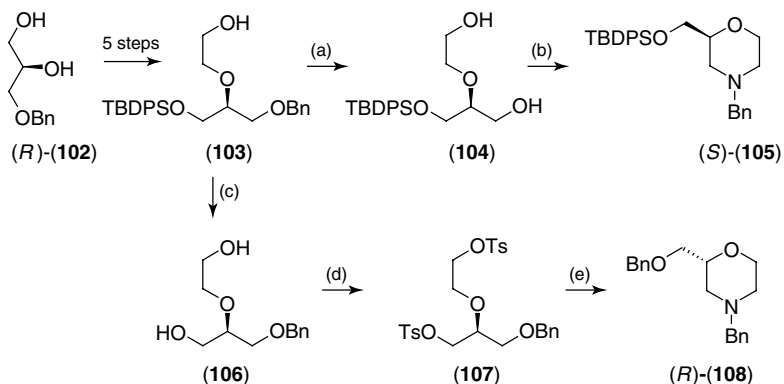
Scheme 7.106

first debenzoylation of **103** to **104** followed by ditosylation and subsequent treatment with benzylamine gave (*S*)-*N*-benzyl-2-*tert*-butyldiphenylsilyloxymethylmorpholine ((*S*)-**105**). On the contrary, when the *tert*-butyldiphenylsilyl (TBDPS) group of **103** was removed followed by ditosylation of **106**, then ring closure of **107** in the presence of benzylamine was performed, and (*R*)-*N*-benzyl-2-benzyloxymethylmorpholine ((*R*)-**108**) could be obtained [211].

Synthesis of (*2R,6R*)-dimethylmorpholine ((*2R,6R*)-**113**) was carried out by a reaction sequence starting with S<sub>N</sub>2 reaction of (*R*)-ethyl lactate ((*R*)-**109**) on the triflate of (*S*)-ethyl lactate ((*S*)-**110**). The conditions, particularly the used solvent, had great influence on the stereochemistry of the reaction. Complete inversion could be achieved by using a 4:1 mixture of *n*-pentane and 1,2-dichloroethane as the solvent and K<sub>2</sub>CO<sub>3</sub> as base. Reduction of diester (*R,R*)-**111** to diol and subsequent mesylation gave dimesylate (*R,R*)-**112**, which could be cyclized with ninefold excess of benzylamine and then debenzylated to (*2R,6R*)-**113** [212].

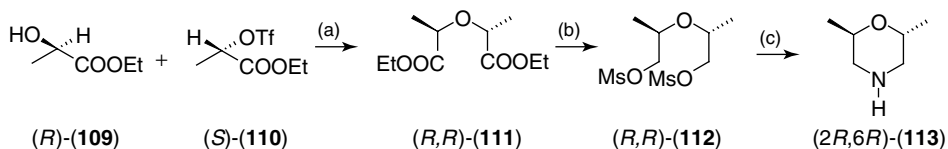
Iodination of **114** using *N*-iodosuccinimide, and subsequent reaction with *N*-Boc-ethanolamine gave compound **115**. Ring closure with base, deprotection and subsequent recrystallization with D-(−)-tartaric acid provided the stereochemically pure product (*R*)-**116** [170, 213].

(*2S,2'S*)-2, 2'-Bimorpholine ((*2S,2'S*)-**119**) could be synthesized from diazido diol **117** via NaH-induced double cyclization of intermediate **118** by intramolecular displacements of the mesyloxy groups with the Boc-protected nitrogens. In an analogous way, the isomeric (*3S,3'S*)-3, 3'-bimorpholine ((*3S,3'S*)-**122**) was prepared



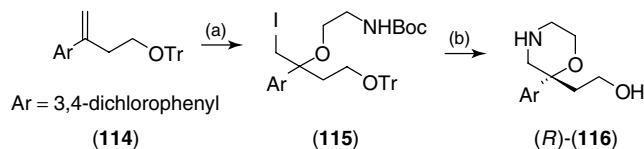
Reagents and conditions: (a)  $\text{H}_2/\text{Pd}-\text{C}$  (98%), (b) 1.  $\text{TsCl}/\text{pyridine}$  (57%), 2.  $\text{BnNH}_2$  (84%), (c)  $\text{HF}/\text{MeCN}$  (87%), (d)  $\text{TsCl}/\text{pyridine}$  (56%), (e)  $\text{BnNH}_2/\text{Na}_2\text{CO}_3/\text{MeCN}$  (85%).

Scheme 7.107



Reagents and conditions: (a)  $\text{K}_2\text{CO}_3/n\text{pentane-1,2-dichloroethane}$  (4:1) (89%), (b) 1.  $\text{LiAlH}_4/\text{Et}_2\text{O}$ , 2.  $\text{MsCl}/\text{pyridine}$  (94%), (c) 1.  $\text{BnNH}_2/\text{dioxane}$  (85%), 2.  $\text{H}_2/\text{Pd}-\text{C}/\text{AcOH}/\text{MeOH}$ .

Scheme 7.108

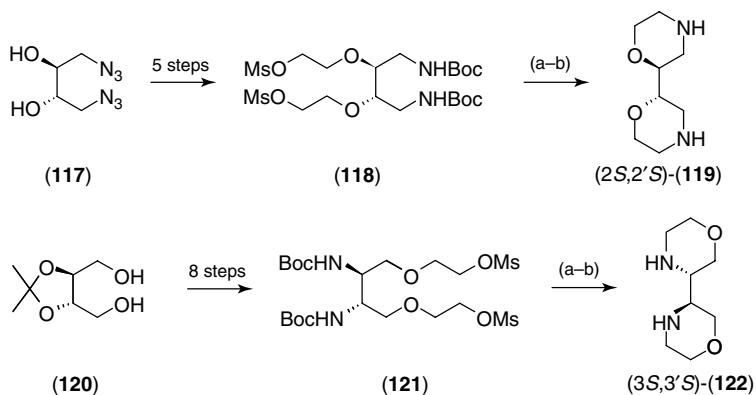


Reagents and conditions: (a) *N*-Boc-ethanolamine/ $\text{NIS}/\text{MeCN}$  (72%), (b) 1.  $\text{NaH}/\text{DMF}$  (77%), 2. 4  $\text{N HCl}/\text{dioxane}/\text{EtOH}$ , 3. recryst. with *D*-(-)-tartaric acid, 4. 1  $\text{N NaOH}$  (82%, 99% ee).

Scheme 7.109

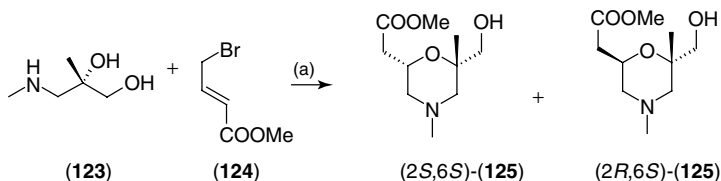
from 120 via the intermediate 121. In both cases, an enantiomeric excess of over 98% was achieved [214].

**Ring Closure by Intramolecular Michael Addition** Intramolecular conjugate addition of either nitrogen or oxygen to  $\alpha,\beta$ -unsaturated ester was employed to morpholine ring formation. Thus, *N*-alkylation of 123 with 124 and subsequent intramolecular



Reagents and conditions: (a) NaH/THF (91–99%),  
(b) 1. TFA/CH<sub>2</sub>Cl<sub>2</sub>, 2. 3 M NaOH/Et<sub>2</sub>O (29–47%, >98% ee).

Scheme 7.110



Reagents and conditions: (a) K<sub>2</sub>CO<sub>3</sub>/Et<sub>2</sub>O/MeOH (100%, dr 6:1).

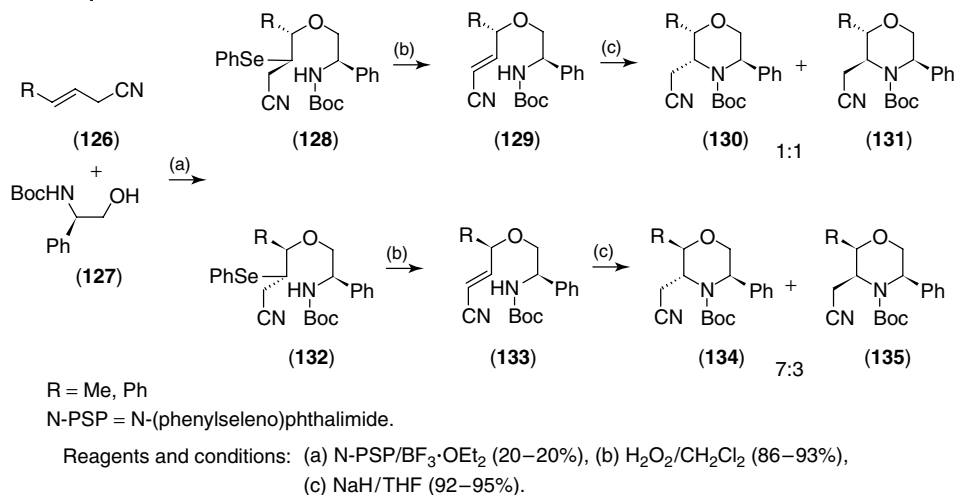
Scheme 7.111

Michael addition afforded a 6:1 mixture of (2S,6S)-125 and (2R,6S)-125, which could be separated by flash chromatography [170, 215].

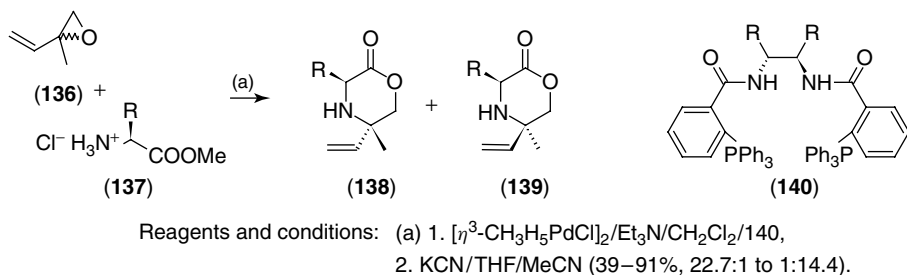
Selenium-promoted addition of (*R*)-phenylglycinol to alkene 126 bearing an electron-withdrawing group gave selenides 128 and 132, which after separation were oxidized to unsaturated nitrile derivatives 129 or 133, respectively. Intramolecular Michael addition of the *trans* isomer 129 gave a 1:1 diastereomeric mixture of 130 and 131, while the *cis* Michael acceptor 133 resulted in a 7:3 mixture of 134 and 135 [216].

**Miscellaneous Methods for Ring Closure** Morpholines 138 and 139 could be synthesized in excellent regio- and stereoselectivities (dr: 22.7:1 to 1:14.4) by opening the epoxide 136 in the presence of enantiomerically pure palladium complexes using ligands 140, and subsequent ring closure with KCN [170, 217].

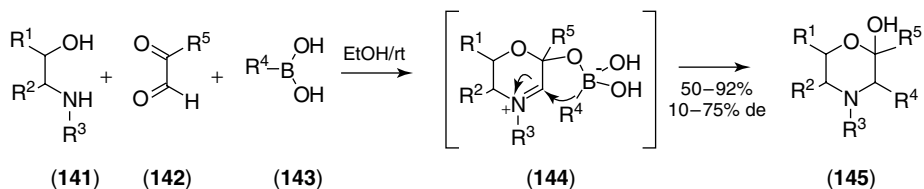
Three-component boro-Mannich reaction between N-protected ethanolamines 141, glyoxal derivatives 142, and boronic acids 143 via a tetracoordinated intermediate (144) provided 2-hydroxymorpholines 145 in various stereoselectivities (10–75% de) depending on the nature of the substituents [170, 218]. The stereoisomer lactols are interconvertible through the ring-opened form, and in some cases, the facile equilibration of the isomers in solution in combination with the crystallization



Scheme 7.112



Scheme 7.113

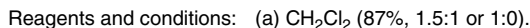


Scheme 7.114

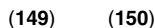
of the desired diastereomer could lead to a crystallization-induced transformation resulting in a single isomer from a complex mixture [219].

Employing a similar method, alkenyl moiety deriving from boronic acid 146 could be introduced to the morpholine ring by reacting with glyoxylic acid and amino alcohol 147. From the obtained diastereomeric mixture, compound (3*S*,5*S*)-148 could be transformed to (3*R*,5*S*)-148 by treatment with triethyl amine, increasing the diastereoselectivity to 100% in this way [170, 220].

Olefins 149 and N-protected ethanolamines 150 reacted via palladium-catalyzed allylic substitution in the presence of a chiral palladium(0) complex to give



Scheme 7.115



Reagents and conditions: (a) Pd(0)/L/THF(20–80%, 16–90% ee).

X = AcO, MeOOCO, *t*BuOOCO.

Scheme 7.116



R<sup>1</sup>= H, Me, *i*Pr, *t*Bu, Ph, naph

$$R^2 = (S)\text{-}i\text{Pr}, (S)\text{-}i\text{Pr}, (R)\text{-Ph}, (R)\text{-BnOCH}_2$$

Reagents and conditions: (a)  $\text{SeO}_2$ /dioxane/D (22–93%).

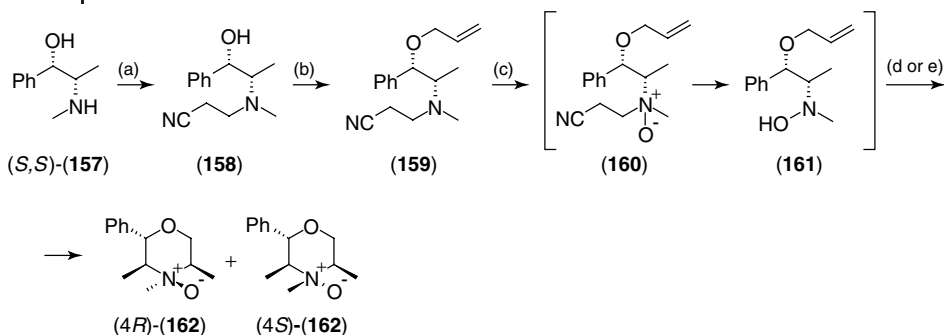
Scheme 7.117

2-vinylmorpholines **151** with moderate to good (16–90%) enantioselectivities [92–94,170, 221, 222].

A SeO<sub>2</sub>-promoted oxidative rearrangement of 2-alkyl and 2-(arylmethyl)oxazolines **152** to unsaturated morpholinones **156** was reported. The proposed mechanism as follows:  $\alpha$ -keto carbonyl derivative **153** formed by SeO<sub>2</sub> oxidation of **152** undergoes Lewis acid-catalyzed ring opening to nitrilium ion **154**, which rearranges to acylium ion **155** followed by a ring closure to **156** [223].

Morpholine *N*-oxides could be stereoselectively prepared from (1*S*,2*S*)-pseudoephedrine ((*S,S*)-**157**). Reaction of (*S,S*)-**157** with acrylonitrile gave the *N*-cyanoethyl derivative **158**, which was then O-alkylated with allyl bromide to **159**. Treatment of **159** with *m*-chloroperbenzoic acid yielded the *N*-oxide **160**, which underwent *in situ* Cope elimination to hydroxylamine **161** and subsequent reverse Cope elimination by heating in dichloromethane, providing morpholine *N*-oxide (4*R*)-**162** as the





Reagents and conditions: (a)  $\text{CH}_2\text{CHCN}/\text{MeOH}$  (100%), (b) 1.  $\text{NaH}/\text{THF}$ , 2.  $\text{CH}_2\text{CHCH}_2\text{Br}$ , (c)  $m\text{-CPBA}/\text{CH}_2\text{Cl}_2/\text{K}_2\text{CO}_3$ , (d)  $\text{CH}_2\text{Cl}_2/\text{D}$  (32%, dr 1:0), (e)  $\text{MeOH}/\text{D}$  (82%, dr 3:2).

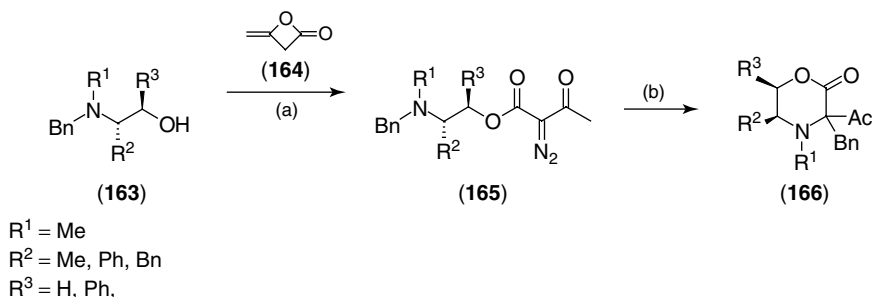
**Scheme 7.118**

single diastereomer. However, heating **161** in methanol gave a 3:2 mixture of the diastereomers (4*R*)-**162** and (4*S*)-**162** [224].

Aminodiazoacetates **165** prepared from amino alcohols **163** by treatment with ketene **164** followed by diazotransfer with  $\text{MsN}_3$  underwent cyclization to morpholinones **166** via copper-catalyzed carbene-transfer reaction with limited diastereoselectivity (dr: 1:1 to 3:3) [225].

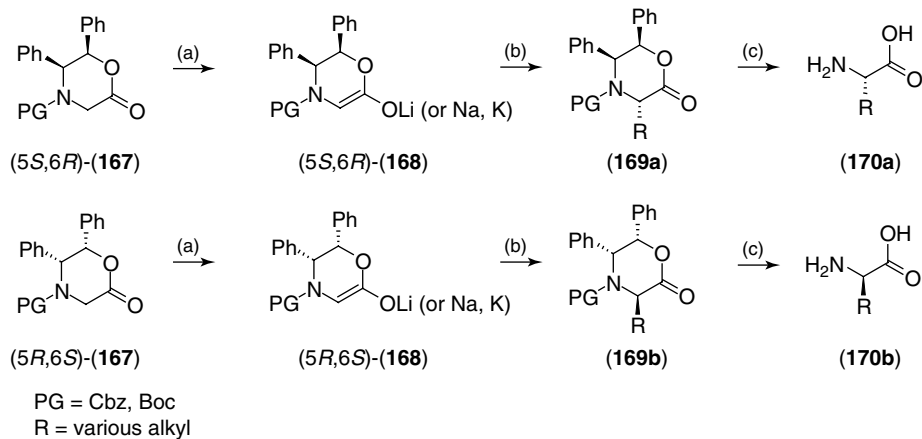
#### 7.1.5.2 Asymmetric Transformations with the Involvement of the Morpholine Ring

**C-Alkylations of Morpholinones** Asymmetric C-alkylation of a stereochemically pure substituted morpholine derivative and subsequent hydrolysis is a widely used strategy for the synthesis of enantiomerically pure amino acids. Thus, enantiomerically pure 5,6-diphenylmorpholin-2-ones **167** (called Williams chiral auxiliaries) can be stereoselectively alkylated on the ring carbon  $\alpha$ -position to the oxo group by reacting the corresponding enolates **168** with alkylhalogenides, thereby providing the products **169** with the newly entered alkyl group *trans* to the phenyl groups. In most cases, high diastereoselectivity was obtained. Alkylated



Reagents and conditions: (a) 1. **164**/ $\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ , 2.  $\text{MeSO}_2\text{N}_3/\text{Et}_3\text{N}/\text{aq MeCN}$  (64–83%), (b)  $\text{Cu-powder}/\text{toluene}/\text{r.f.}$  (70–71%, dr 1:1 to 3:1).

**Scheme 7.119**



Reagents and conditions: (a) LiHMDS or NaHMDS or KHMDS/THF (crown ether),  
(b) RX (>90% de), (c) H<sub>2</sub>/Pd–C or PdCl<sub>2</sub>.

Scheme 7.120

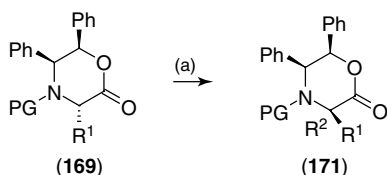
morpholinones, after hydrogenolysis, could be transformed to the corresponding amino acids **170** [175, 226–237].

Other differently substituted, optically active morpholinones could also be alkylated at the  $\alpha$ -position with various stereoselectivities [196, 238, 239].

Dialkylation at 2-position could be diastereoselectively achieved by deprotonation of monoalkylated derivative **169** and subsequent reaction with various nucleophiles affording **171** [240, 241].

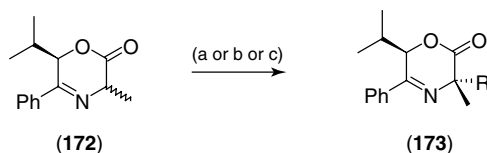
Najera *et al.* used mild PTC conditions in the presence of a weak base for diastereoselective alkylation of morpholinones **172** with activated halides. Pd-catalyzed allylation of the same substrate was also performed by reacting **172** with allyl carbonates in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> and 1,2-bis(diphenylphosphino)ethane (dppe) to give the product **173** [242].

However, in the alkylation reactions of **172** with inactivated alkyl halide, the PTC conditions were not suitable; instead, 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) was used as the base. In this case, a competitive O-alkylation was observed, which could be suppressed by adding LiI [243].



Reagents and conditions: (a) KHMDS/R<sup>2</sup>X/THF (80–90%, 100% de).

Scheme 7.121



R = for (a) or (b): (subst)allyl, propargyl, Bn, EtCOOCH<sub>2</sub> for (c): Et, *i*Pr, *n*Bu, *i*Bu.

Reagents and conditions: (a) RX/K<sub>2</sub>CO<sub>3</sub>/*n*Bu<sub>4</sub>NBr/MeCN or CH<sub>2</sub>Cl<sub>2</sub>/rt (60–75%, >92% de),  
 (b) allyl carbonates/Pd(PPh<sub>3</sub>)<sub>4</sub>/dppe/THF/rt (53–65%, >91% de),  
 (c) RX/BEMP or DBU/ (LiI)/NMP (28–65%, >96% de).

dppe: 1,2-bis(diphenylphosphino)ethane.

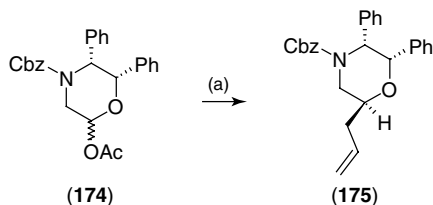
BEMP: 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine.

DBU: 1,8-diazabicyclo(5.4.0)undec-7-ene.

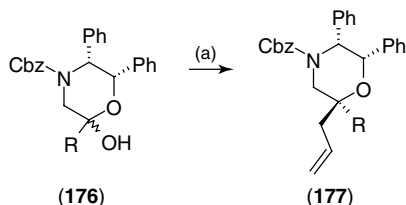
#### Scheme 7.122

Besides halogenides, allyl silanes are also suitable reagents for allylation of the morpholine ring. Reaction of acetoxy hemiacetals **174** or acetals **176** with allyltrimethylsilane in the presence of BF<sub>3</sub>·OEt<sub>2</sub> or TiCl<sub>4</sub>, gave allylated products **175** or **177** as single diastereomers, respectively [244, 245]. The same methods were applied to chiral morpholines substituted in a different way [246, 247].

Titanium, aluminum, or boron enolates of diphenylmorpholinone **167** could be reacted with orthoester, aldimine, or aldehyde, affording stereoselectively the corresponding alkylated product **178**, **179**, or **180**, respectively, with the entering group *trans* to the phenyl groups. In case of compounds **179** and **180**, a 3.1:1 or 8:1 diastereomeric mixture was obtained, respectively, with regard to the newly formed chiral center in the side chain [248–250].



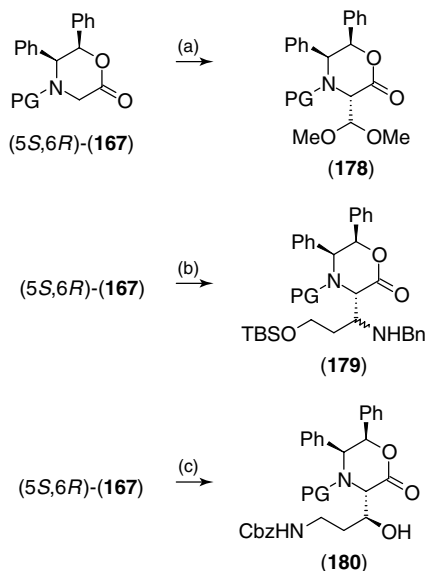
Reagents and conditions: (a) allyltrimethylsilane/BF<sub>3</sub>·Et<sub>2</sub>O/MeCN (98%).



R = alkyl

Reagents and conditions: (a) allyltrimethylsilane/TiCl<sub>4</sub>/CH<sub>2</sub>Cl<sub>2</sub> (65–67%).

#### Scheme 7.123



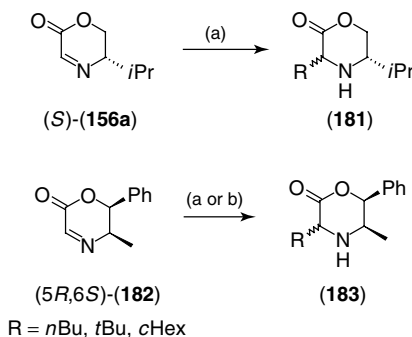
Reagents and conditions: (a) 1.  $\text{TiCl}_4/\text{Et}_3\text{N}$ , 2.  $(\text{MeO})_3\text{CH}/\text{CH}_2\text{Cl}_2$  (94%),  
 (b) 1.  $\text{LiHMDS}/\text{THF}$ , 2.  $\text{Me}_2\text{AlCl}$ , 3.  $\text{TBSO}(\text{CH}_2)_2\text{CH}=\text{NBn}$  (60%, dr 3.1:1),  
 (c) 1.  $\text{Bu}_2\text{BOTf}/\text{Et}_3\text{N}/\text{CH}_2\text{Cl}_2$ , 2.  $\text{Cbz}(\text{CH}_2)_2\text{CHO}$  (69%, dr 8:1).

**Scheme 7.124**

Alkyl radicals generated from alkyl iodides were added to the imine bond in unsaturated morpholinones (*S*)-**156a** and (5*R*,6*S*)-**182** in the presence of  $\text{Bu}_3\text{SnH}/\text{AIBN}$ . In the reaction of disubstituted morpholinone (5*R*,6*S*)-**182** higher diastereoselectivity than that of (*S*)-**156a** was observed, affording the products **181** and **183**, respectively, by preferential attack *anti* with respect to the substituents. Complete stereoselectivity, but lower yield, was obtained by alkylating compound (5*R*,6*S*)-**182** at low temperature with  $\text{Et}_3\text{B}$  as complexing agent and a radical initiator [251].

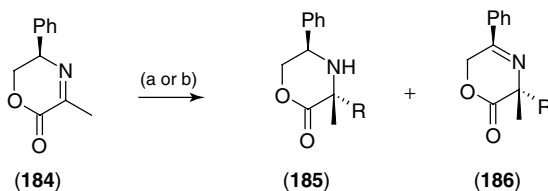
Radical addition to morpholines **184** was performed in the presence of  $\text{BF}_3 \cdot \text{OEt}$  as Lewis acid using triethyl borane as the radical initiator providing the ethylated product **185** ( $\text{R} = \text{Et}$ ) and ethylated imine **186** ( $\text{R} = i\text{Pr}$ ). Isopropyl radical addition proceeded smoothly in the presence of isopropyl iodide [252]. Under the same conditions, except using Lewis acid, radical addition to unsaturated 5,6-diphenylmorpholinone *N*-oxides were carried out in high (95%) diastereoselectivity [253].

**Arylations** Stereoselective introduction of aryl groups to position 3 was performed on substrate **187** in two alternative ways. Reaction of **187** with various aromatic compounds possessing bromine, methoxy or hydroxy groups as the substituents in the presence of TFA or reaction of boronic acid gave the corresponding substituted products **188** in 60–90% de [170, 254].



Reagents and conditions: (a)  $\text{RI}/n\text{Bu}_3\text{SnH}/\text{AIBN}/\text{benzene}/80^\circ\text{C}$   
 (41–62%, dr 55:45 to 60:40 for 181, 75:25 to 87:13 for 183),  
 (b)  $\text{RI}/\text{Et}_3\text{B}/\text{CH}_2\text{Cl}_2/-40^\circ\text{C}$  (25–27%, dr 90:10 to 100:0).

Scheme 7.125

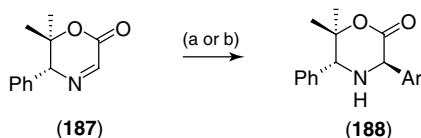


Reagents and conditions: (a)  $\text{BF}_3 \cdot \text{OEt}_2/\text{Et}_3\text{B}/\text{hexane}/\text{CH}_2\text{Cl}_2/0^\circ\text{C-rfx}$   
 (42–74%, 81–87% de, 185:186=10:6 to 10:1),  
 (b)  $\text{BF}_3 \cdot \text{OEt}_2/i\text{PrI}/\text{Et}_3\text{B}/\text{hexane}/\text{CH}_2\text{Cl}_2/\text{rfx}$   
 (185: 61%, 82% de, 186: 15%).

Scheme 7.126

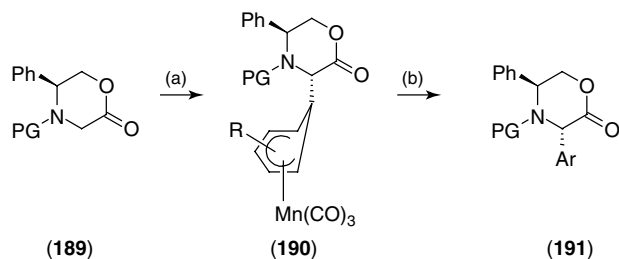
Arylation of oxazinones **189** was achieved by treatment of the corresponding enolates with (arene) $\text{Mn}(\text{CO})_3$  complexes, followed by oxidative demetalation of the intermediate substituted cyclohexadienyl- $\text{Mn}(\text{CO})_3$  complex **190** to afford arylmorpholinones **191** in 75–99% de [255].

**Stereoselective Reductions** Reduction of alkylidene substituents in compounds **192** or **194** to the alkyl ones could be carried out either by hydrogen gas in the



Reagents and conditions: (a)  $\text{TFA}/\text{CH}_2\text{Cl}_2/\text{ArH}$  (83–98%, 60–100% de),  
 (b)  $4\text{-MeOC}_6\text{H}_4\text{B}(\text{OH})_2/\text{Cl}(\text{CH}_2)_2\text{Cl}/\text{TFA}$  (85%, 90% de).

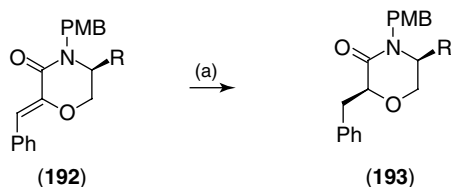
Scheme 7.127



PG = Boc, Cbz

Reagents and conditions: (a) 1. NaHMDS/THF, 2. (arene) $\text{Mn}(\text{CO})_5^+\text{PF}_6^-$ ,  
(b) NBS/ $\text{Et}_2\text{O}$  (44–65%, 75–99% de).

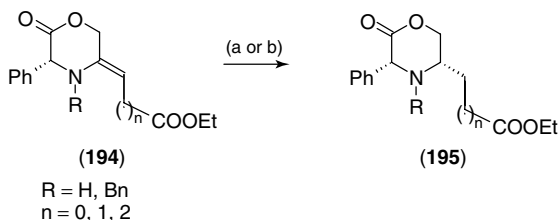
Scheme 7.128



R = *i*Bu, *s*Bu

Reagents and conditions: (a)  $\text{H}_2$ /Pd-C (97–98%, dr 8:1 to 10:1).

Scheme 7.129



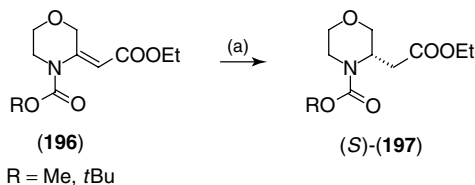
R = H, Bn  
n = 0, 1, 2

Reagents and conditions: (a)  $\text{BH}_3$ /THF/MeCN (76–80%, 90–92% de),  
(b)  $\text{NaBH}_4$ /AcOH/MeCN/TFA (71%, 94% de).

Scheme 7.130

presence of a Pd-C catalyst or with  $\text{NaBH}_4$ , or using the borane-THF complex as the reducing agent, providing the *cis* products **193** or **195**, respectively, in good stereoselectivity [186, 256].

Iridium complex-catalyzed asymmetric hydrogenation of achiral exocyclic double bond in **196** allowed the introduction of a chiral center on an achiral structure. The reaction was performed in the presence of chiral phosphine ligands and afforded the corresponding saturated derivatives (*S*)-**197** in good (79–85.5%) enantiomeric excesses [257].



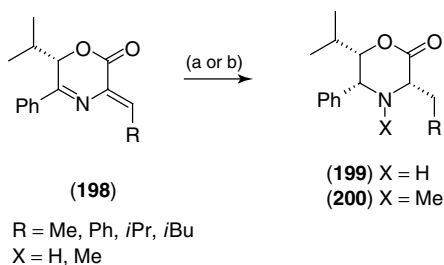
Reagents and conditions: (a) 40–50 bar  $H_2$ /((COD)Ir(Cl))<sub>2</sub>/(S)-BINAP or (S)-TolBINAP (100% conv, 79–85.5% ee).

**Scheme 7.131**

Both endo- and exocyclic double bond in **198** was saturated using  $PtO_2$  as the catalyst to **199** in excellent stereoselectivities (dr: 96:4 to 97:3). In the presence of formaldehyde, N-methylated derivative **200** was obtained with diastereomeric ratios of 91:9 to 98:2 [192, 193].

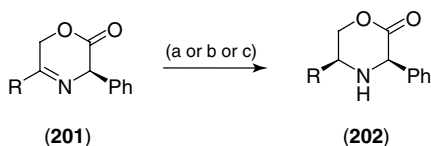
Diastereoselective reductions of chiral unsaturated morpholinones **201** to **202** were carried out by three different methods.  $PtO_2/H_2$ ,  $NaBH(OAc)_3$ , or  $BH_3$  proved to be the suitable reducing agent [256, 258].

For saturation of **203** to **204** or **205** to **206**, respectively, either  $PdCl_2$  or  $Pd-C$  was applied successfully as hydrogenation catalyst [183, 259, 260].



Reagents and conditions: (a)  $PtO_2/H_2/MeOH$  (62–95%, dr 96:4 to 97:3),  
(b)  $PtO_2/H_2/CH_2O/MeOH$  (63–75%, dr 91:9 to 98:2).

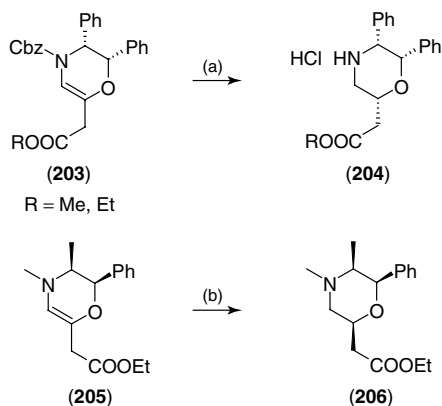
**Scheme 7.132**



R = Me, Et, *i*Pr, *n*Bu, *t*Bu

Reagents and conditions: (a)  $H_2/PtO_2/MeOH$  (73–89%, *cis:trans* = 83:17 to 93:7),  
(b)  $NaBH(OAc)_3/TMSCl$  (73–83%, 60–86% de),  
(c)  $BH_3 \cdot THF/MeCN$  (71–93%, 84–98% de).

**Scheme 7.133**



Reagents and conditions: (a)  $\text{H}_2/\text{PdCl}_2/\text{EtOH}/\text{HCl}$  (99%, dr 96:4),  
 (b)  $\text{H}_2/\text{Pd}-\text{C}/\text{EtOAc}$  (quant).

Scheme 7.134

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## 8

# Asymmetric Synthesis of Seven-Membered Rings with More Than One Heteroatom

Jacques Royer

### 8.1

#### Diazepines

The diazepines represent a large class of compounds for which many syntheses were described in the literature. They are natural and synthetic products with interesting biological activity. Among diazepines, the 1,2-diazepine are rare while 1,4-diazepines are the most often reported isomers. The 1,3-diazepines are urea or amine derivatives and their preparation was on the basis of the access to these functional groups. Concerning the 1,4-diazepines, many methods of preparation were reported but most of them were derived from amino acids, which furthermore allowed the introduction of chirality.

#### 8.1.1

##### 1,2-Diazepines

Asymmetric synthesis of chiral 1,2-diazepine is rarely reported in the literature though some of them are known as *biologically active compounds*. For example, talampanel was found to possess potential antiepileptic, neuroprotectant and skeletal muscle relaxant activities [1] and cilazapril (Figure 8.1) is effective in the treatment of hypertension and other cardiovascular disorders [2].

A very few methods were reported and were classical ones on the basis of a unique strategy. They are mainly prepared through the bis-condensation of a hydrazine to a 1,5-dicarbonyl derivative. The latter is thus the chiral part of the molecule and no new chiral center is formed during the process. The bis-condensation may be attained during a one-pot reaction; for example, the pyrrolodiazepine **3**, a potential acetylcholine esterase (ACE) inhibitor, was prepared through the reaction of a monosubstituted unprotected hydrazine with the cetoacide derivative **1** [3] to give the required heterocycle **2** in modest yield (Scheme 8.1).



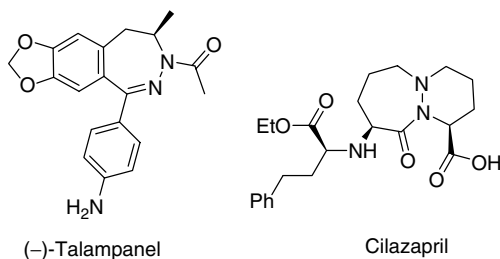
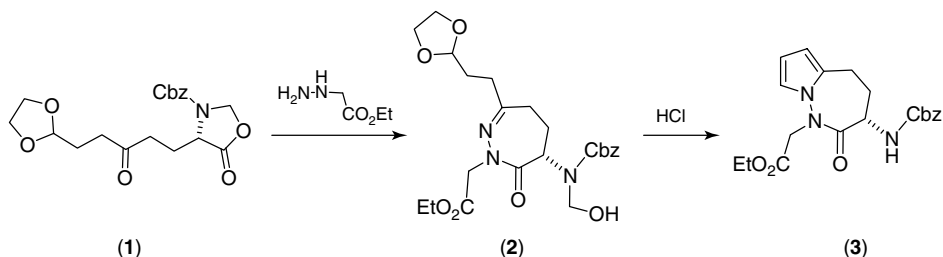


Fig. 8.1 Biologically active 1,2-diazepines.



Scheme 8.1

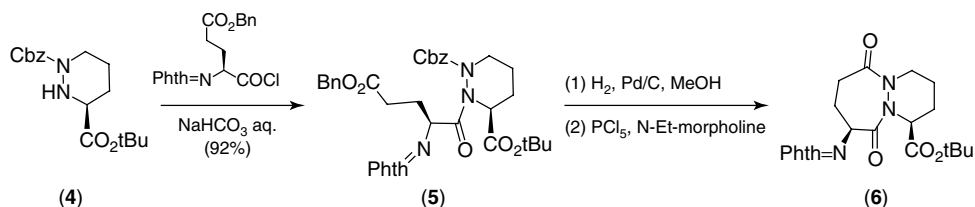
Indeed, a two-step process seemed more efficient and is currently used. The 1,5-dicarbonyl compound may be a suitably protected glutamic acid or a synthetic product. The hydrazine part may also be chiral as in the following two examples. In these cases, devoted to the preparation of interleukin-1 $\beta$  converting enzyme (ICE) inhibitors the condensation is sequential and ends up by lactamization [4, 5] or by reductive alkylation [6] (Scheme 8.2).

In the preparation of **9**, a sugar (D-xylose) was the starting material, which was treated with a monoprotected hydrazine (Scheme 8.3). The basic treatment of mesitylsulfonate **7** gave in good yield and without loss of optical purity, the seven-membered ring **8** probably via the intermediate formation of an epoxide [7].

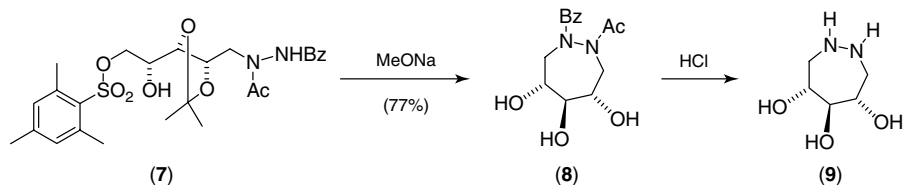
### 8.1.2

#### 1,3-Diazepines

These heterocycles are widely represented by compounds found as potent HIV protease inhibitors. This is particularly the case for cyclic ureas such as DMP 323



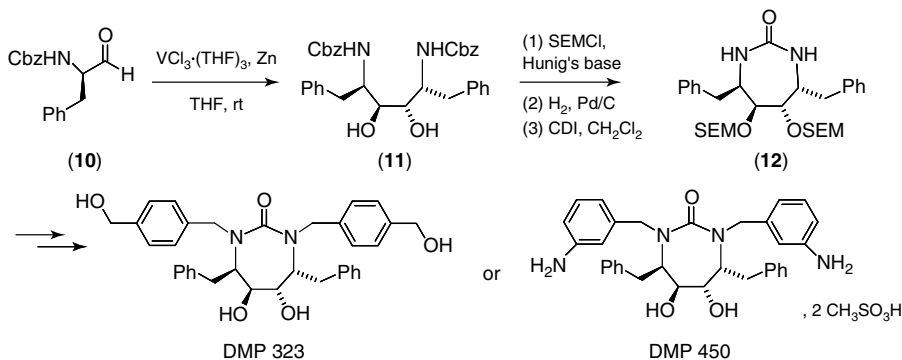
Scheme 8.2



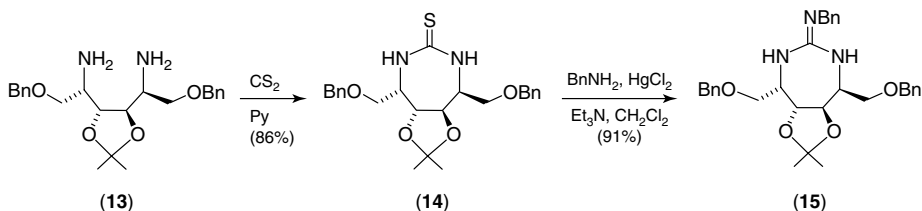
Scheme 8.3

and DMP 450. The main characteristics of their structures are the seven-membered ring, the cyclic urea functionality, and a C2 symmetry. The synthesis of these compounds and their analogs is, in most cases, the same and consists of the preparation of a chiral 1,4-diamine, which is transformed into a cyclic urea with a suitable reagent, such as carbonyldiimidazole, [8] phosgene [9], trialkylorthocarbonate [10], or dimethylcyanodithioiminocarbonate via the cyanoguanidine [11]. The following sequence [8c] (Scheme 8.4) is representative of the published syntheses. In this example, the chiral diamine **11** was obtained through the low valent vanadium pinacol coupling with the aldehyde **10** derived from phenylalanine. Several examples are also reported on the preparation of analogous diamines from tartaric acid or sugars.

The preparation of structurally related C2-symmetric guanidines was also reported. These compounds are potent glycosidase inhibitors. Diamine **13** (Scheme 8.5), derived from mannitol, when treated with carbon disulfide in pyridine gave thiourea **14**, which could be transformed to guanidine **15** [12].



Scheme 8.4



Scheme 8.5



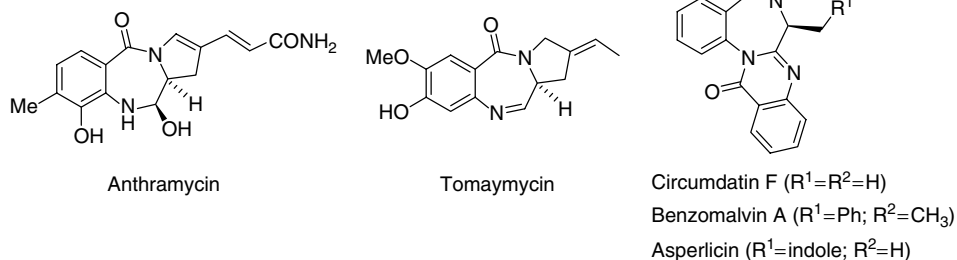


Fig. 8.2 Natural benzodiazepines.

## 8.1.3

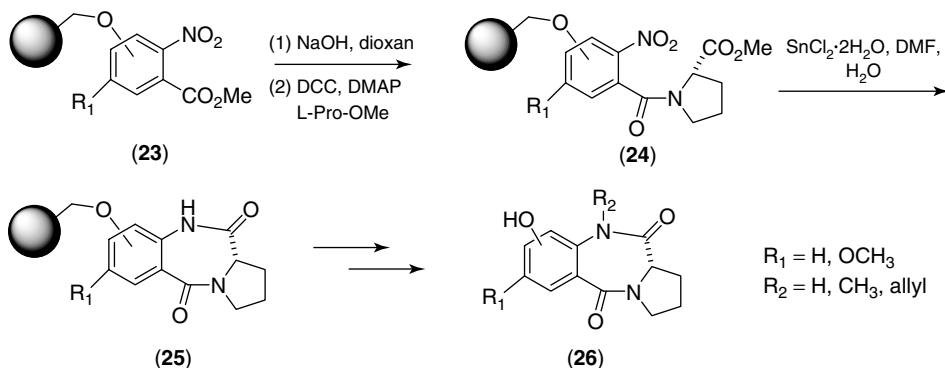
## 1,4-Diazepines

These heterocycles are of great importance as a very impressive number of 1,4-diazepines are biologically active products. Among them, the benzodiazepine series is a very well known series and has been proved to exhibit important activities ranging from those of central nervous system (CNS) to those of anticancer agents, while antibiotics, anti-HIV, or cardiovascular agents were also reported. Several natural products were also known and some of them are depicted in Figure 8.2.

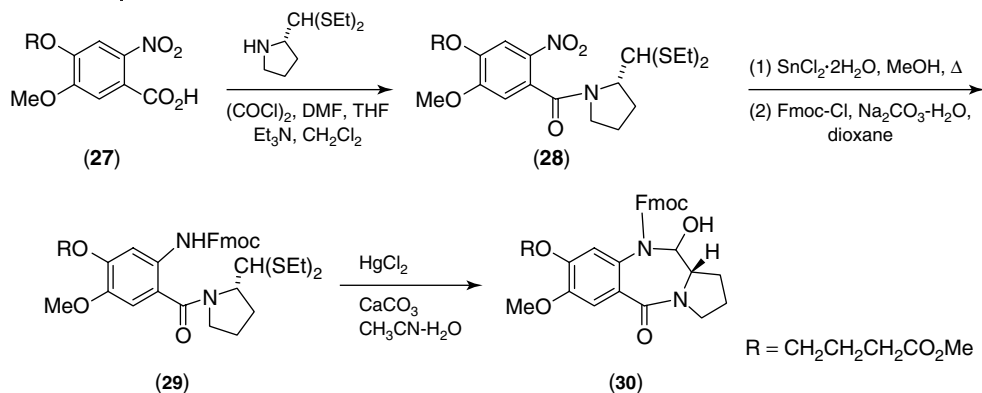
Because of the huge importance of this series of products, a very rich literature exists describing numerous asymmetric syntheses. Indeed, compared to the number of papers dealing with 1,4-diazepines, the number of available methods of preparation is not so large; the more general and recent ones are gathered below. Because of their paramount importance, the benzodiazepine products are described separately.

## 8.1.3.1 1,4-Benzodiazepines

**Via 2-Nitrobenzoic Acid Derivatives or Isatoic Anhydride** Formally, a benzodiazepine is the result of the condensation between anthranilic acid and an  $\alpha$ -amino acid. This



Scheme 8.9



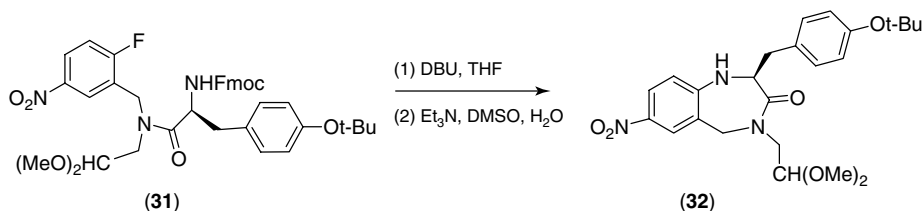
Scheme 8.10

methodology is not directly used but derived methods were more often described. A 2-nitrobenzoic acid (or ester or acyl chloride) [16] is usually condensed with an amino acid through classical coupling methods as in the recent example depicted in Scheme 8.9 showing the possible use of a solid phase synthesis. The reduction of the nitro group then allowed cyclization by lactamization [16b]. The same type of reaction was also described starting from an *o*-azido benzoic acid [17].

The use of isatoic anhydride (substituted or not) as a more activated starting material has been reported [18]. The condensation with an  $\alpha$ -amino acid may be conducted in a single step in refluxing pyridine [19].

The preparation of anthramycin, tomaymycin, and analogs and more generally of antitumor- and gene-targeted drugs possessing an imine or *N*, *O*-acetal (or hemiacetal) function [20] requires the use of a chiral aminoaldehyde instead of the parent amino acid. The strategy remained the same and is illustrated in Scheme 8.10 [20d]. The nitrobenzoic acid **27** was first coupled with a protected aldehyde derived from proline and the nitro group was reduced to a primary amino group. The Fmoc protection, followed by the selective aldehyde regeneration allowed the cyclization to occur with formation of the benzodiazepine ring.

**Via an  $\text{S}_{\text{N}}\text{Ar}$  Reaction** Some authors described the synthesis of benzodiazepines through an  $\text{S}_{\text{N}}\text{Ar}$  reaction. The attachment of the appropriate amino acid to a benzoic acid derivative was followed by the  $\text{S}_{\text{N}}\text{Ar}$  reaction. This reaction usually necessitated the presence of a fluorine atom and a nitro activating group. This may



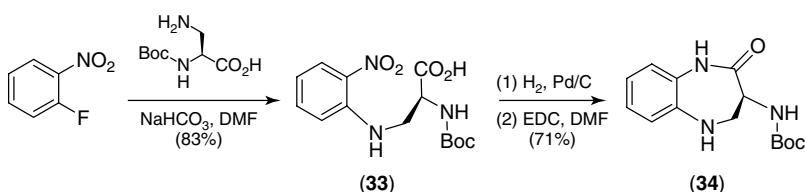
Scheme 8.11

allow the specific substituents on the aromatic ring to be suitably positioned. The  $S_NAr$  reaction could occur for the cyclization step or for the introduction of the amino acid moiety onto the aromatic ring. The sequence described in Scheme 8.11 used the  $S_NAr$  reaction as the final cyclization step and furnished a benzodiazepine as a mimetic of type-II  $\beta$ -turn [21].

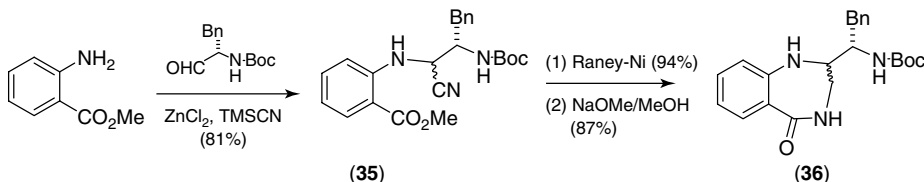
To achieve the cyclization, an intramolecular CuI-catalyzed arylation according to the Ullmann reaction has also been described [22]. For instance, 1,5-benzodiazepines **34** (Scheme 8.12) has been prepared as a peptidomimetic with caspase-1 inhibitor properties. Along with this synthesis the  $S_NAr$  reaction of 1-fluoro-2-nitrobenzene with Boc-(L)-2,3-diamino propionic acid afforded amino acid **33** [23]. The latter was reduced and then cyclized to give **34**.

**Via a Strecker Reaction** R. Herranz proposed an original strategy of preparation of 1,4-benzodiazepines using an aminonitrile route. Methyl anthranilate was condensed with a chiral N-Boc-amino aldehyde in the presence of TMSCN to give the aminonitrile **35** in good yield but as a 2:1 mixture of stereoisomers (Scheme 8.13). Reduction (Raney Ni) and cyclization allowed the isolation of the desired benzodiazepines **36**, which were chromatographically resolved to both epimers [24].

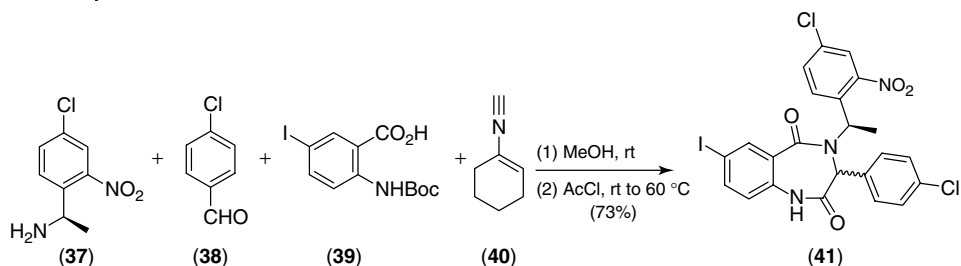
**Ugi Reaction** In a series of papers devoted to the enantioselective preparation of 1,4-benzodiazepine-2,5-diones as Hdm2 antagonist, Lu and coworkers [25] reported the use of a Ugi reaction according to the process established by Armstrong [26], which used 1-cyclohexyl isocyanide. The Ugi reaction was followed by *in situ* cyclization to the diaza heterocycle. Chiral amine **37**, benzaldehyde **38**, and acid **39** were condensed with isocyanocyclohexene **40** for two days at room temperature and followed by cyclization with acetyl chloride to give the expected diazepine **41** in good yield but as a 1:1 mixture of epimers, which could be separated by chromatography (Scheme 8.14).



Scheme 8.12



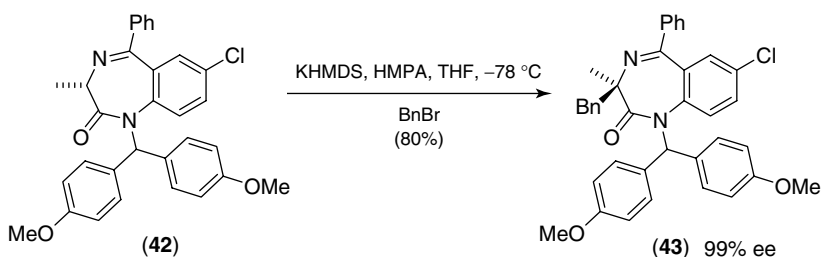
Scheme 8.13



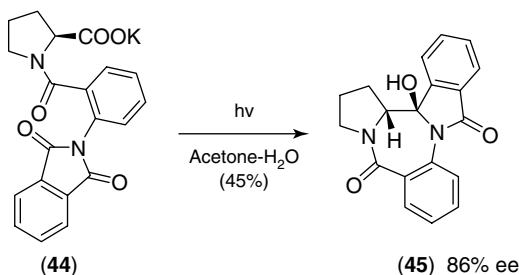
Scheme 8.14

**Diastereoselective Alkylation** Carlier reported the enantioselective synthesis of diversely substituted quaternary 1,4-benzodiazepine -2-one **43** by alkylation of chiral diazepine **42** following the concept of memory of chirality defined by K. Fuji. The use of the di-(*p*-anisyl)methyl (DAM) group on the lactam nitrogen was proved to provide quaternary benzodiazepines in higher enantioselectivities and yields upon the deprotonation/alkylation sequence as ee > 99% was obtained as in the following example (Scheme 8.15) [27].

**Photocyclization** The same concept of memory of chirality was invoked in a photochemical process that may involve a 1,7-triplet biradical. The proline derived potassium salt **44** gave the pyrrolobenzodiazepine **45** upon a decarboxylative photocyclization (Scheme 8.16). A high degree of chirality was retained as compound **45** was obtained with 86% ee [28].



Scheme 8.15

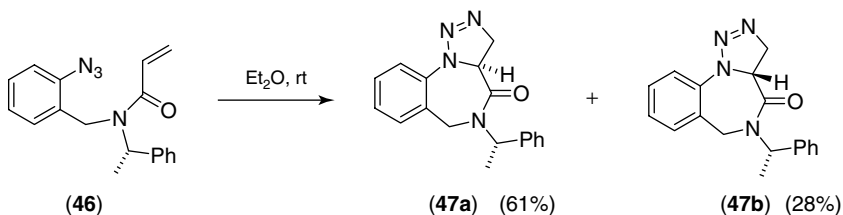


Scheme 8.16

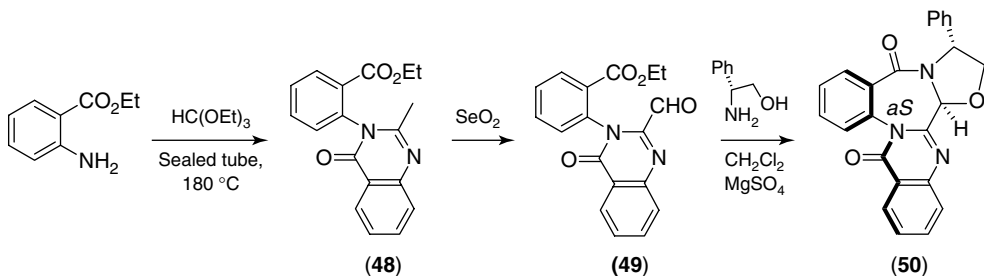
**1,3-Dipolar Cycloaddition** Homochiral *N*-alkenoyl azide **46** (Scheme 8.17), easily obtained from the corresponding amines via diazotation, underwent an intramolecular 3+2 cycloaddition to furnish original triazol-benzodiazepine-4-ones **47a,b**. Under very mild conditions, and thanks to the presence of a chiral appendage on nitrogen, diastereomers were obtained and could be separated. Though the method was somewhat hampered by a modest diastereoselectivity, it offered an original and straightforward approach to this type of compounds [29].

**Meyers' Bicyclic Lactam Strategy** In efforts toward the asymmetric synthesis of natural products of the circumdatin series, the Meyers' bicyclic lactam strategy was used to attain the benzodiazepine skeleton in very good diastereoselectivity albeit low yield. The methyl-quinazoline **48** was easily prepared by the condensation of two molecules of anthranilic acid and then oxidized to the aldehyde **49** with selenium oxide (Scheme 8.18). Then aldehyde **49** was condensed with phenylglycinol to afford the quinazalone–benzodiazepine **50** in a modest 25% yield but an excellent 95% de [30]. Importantly, the conditions allowed the formation of the natural product biaryl *aS* configuration.

**Nitrilium Insertion** An original new approach to pyrrolobenzodiazepines (PDB) known as *antitumor compounds* and their heterocycle-fused pyrrolo-diazepine analogs appeared in 2005 [31]. In this approach, the cyclization process consisted in intramolecularly trapping of a nitrilium species by an electron-enriched aromatic group. Proline derivative **51** was readily obtained by classical amino acid coupling and transformed to the methoxyamide **52**. Hypervalent iodine (phenyliodine bis(trifluoroacetate)) (PIFA) (Scheme 8.19) oxidation was found to be effective

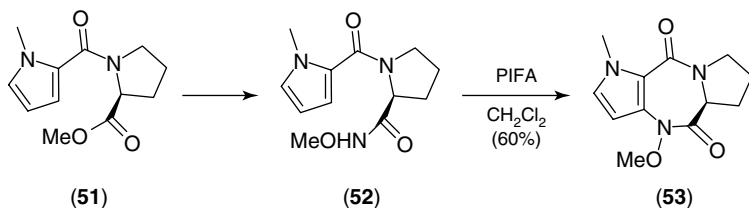


Scheme 8.17



Scheme 8.18





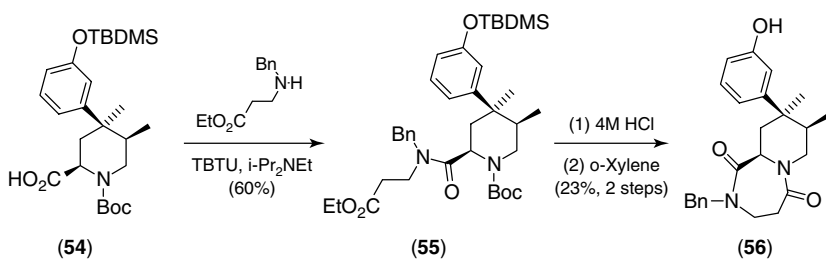
Scheme 8.19

to form the positively charged *N*-acetyl nitrenium species that was trapped *in situ* to form the pyrrolo benzodiazepine (PBD) analog 53.

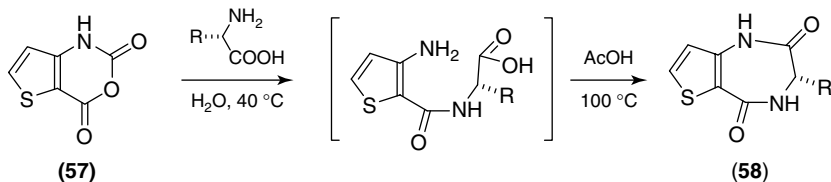
### 8.1.3.2 Other 1,4-Diazepines

**Amino Acid Strategies** The methods already described in the benzodiazepine series could be used in the preparation of diazepines in general. The more general and obvious method is the condensation of a  $\beta$ -amino acid with an  $\alpha$ -amino acid; both of them could be asymmetric [32] but more frequently only the  $\alpha$ -amino acid is the chiral partner with no formation of a new chiral center [33]. In the following example (Scheme 8.20), the preparation of a novel  $\mu$ -opioid receptor antagonist was on the basis of the asymmetric access to the highly substituted pipecolic acid 54, coupled with 3-amino propionic acid and cyclized to form the diazepine skeleton [34].

The amino acid could be condensed with a 3-haloamine or 3-acrylonitrile [35] giving rise after function manipulations to intermediary derivatives ready to cyclize into the diazepine ring. The final cyclization is generally a lactamization, as described above, but a Mitsunobu reaction with a serine hydroxyl was reported [36].



Scheme 8.20



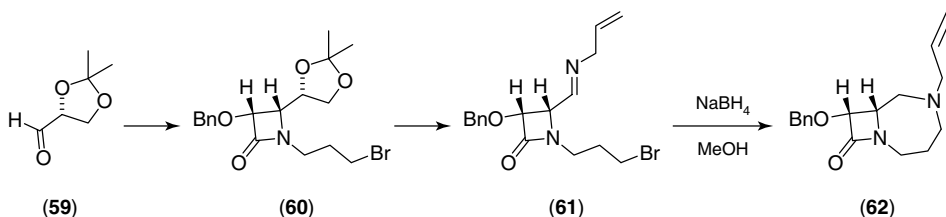
Scheme 8.21

In a recent paper, Martinez [37] described the reaction of various amino acids with thiaisatoic anhydride (Scheme 8.21). This two-step, one-pot procedure allowed an expeditive and efficient access to thienodiazepines.

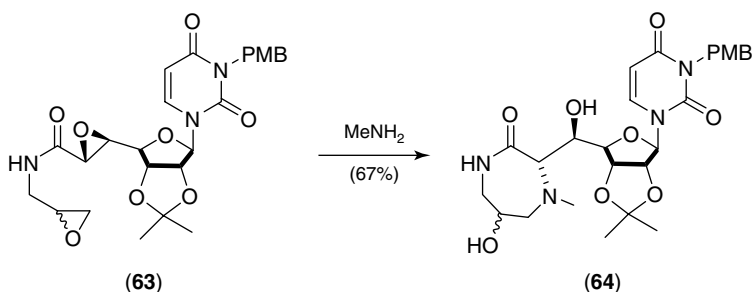
**Cyclization through a Nitrogen Nucleophilic Displacement** Several diazepines were prepared through a non-amino acid route. In most of these cases, the formation of a carbon–nitrogen bond was the ultimate cyclization step giving rise to the diazepine skeleton [38]. In the following example (Scheme 8.22), 1,4-diazepane annulated  $\beta$ -lactam was obtained by construction of the diazepine ring on the  $\beta$ -lactam. The (*R*)-glyceraldehyde acetonide (**59**) was the starting material for the  $\beta$ -lactam ring formation through the Staudinger reaction. The oxidative cleavage of the diol and alkylation of the nitrogen of the lactam allowed the formation of a bromo aldehyde and then the bromo imine **61**. The latter was reduced with  $\text{NaBH}_4$  to allow the cyclization and furnish the optically active bicyclic  $\beta$ -lactam **62** [39].

Cyclization through a Strecker type reaction was used in the total synthesis of manzacidin A and C reported in 2000 by Ohfuné [40]. In the synthesis of liposidomycins, a new class of complex nucleoside-type antibiotics, the construction of the diazepinone ring was attained by the double opening of bis-epoxide **63** by methylamine as shown in Scheme 8.23 [41].

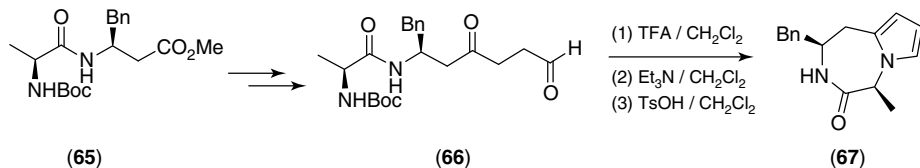
**Paal–Knorr Cyclization** Lubell has described the synthesis of pyrrolodiazepinone via an intramolecular Paal–Knorr condensation [42]. The synthesis started by the condensation of an  $\alpha$ - and a  $\beta$ -amino acid to **65** (Scheme 8.24), which was transformed to the homoallylic ketone **66** precursor of 4-keto aldehyde or 1,4



Scheme 8.22



Scheme 8.23



Scheme 8.24

diketone through oxidative processes. Deprotection of the nitrogen allowed the Paal–Knorr condensation to occur in good yield.

## 8.2

### Oxazepines

Oxazepines constitute a large family of compounds while not so large as the diazepine ones. Their preparations are interesting and basically different from those of diazepine derivatives.

#### 8.2.1

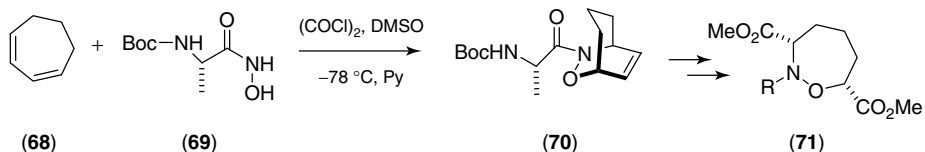
##### 1,2-Oxazepine

This type of compounds has mainly been prepared by cycloaddition: 4+2, 3+2 and 3+4 cycloadditions were found to be used to give bicyclic derivatives with good diastereoselectivities.

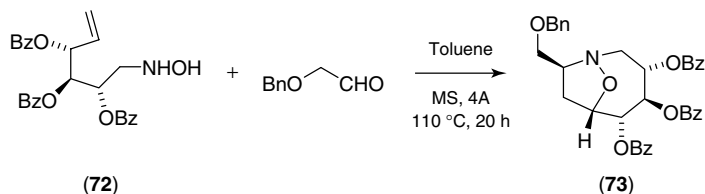
##### 8.2.1.1 Diels–Alder Cycloaddition

Several workers reported that Diels–Alder cycloaddition of cycloheptatriene with chiral acyl- or chloronitroso derivatives afforded oxaza-bicyclo[3.2.2] nonanes in good yields and stereoselectivities. Lallemand [43] investigated various acylnitroso compounds (derived from alanine, mandelic acid, and ribose). The hydroxamic acid **69**, derived from alanine (Scheme 8.25), was reported to be oxidized under Swern conditions and *in situ* cyclized with cycloheptatriene to give the bicycloadduct **70** as a 3:1 mixture of stereoisomers [44]. Recrystallization of the mixture allowed the diastereomeric ratio to be raised to 50:1, and was followed by deprotection and oxidative cleavage of the double bond to furnish the diester **71**.

During the preparation of the same type of oxaza-bicyclo compounds, Wang [45] reported that both the acylnitroso and the chloronitroso compounds derived from



Scheme 8.25



Scheme 8.26

the same ketopinic acid added to cycloheptadiene to give the desired compounds in good yield and excellent but inverted diastereoselectivity.

### 8.2.1.2 Intramolecular 3+2 Cycloaddition

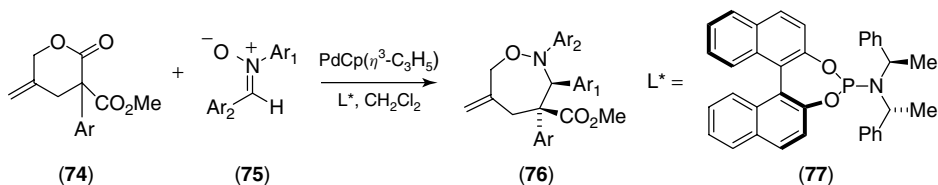
Several papers reported the intramolecular 3+2 cycloaddition between a nitron and an olefine [46]. The condensation of hydroxylamine **72**, derived from methyl  $\alpha$ -D-glucopyranose, with 2-(benzyloxy)-acetaldehyde in dry toluene gave cycloadduct **73** as the only isolable product (Scheme 8.26).

### 8.2.1.3 Pd-Catalyzed 4+3 Cycloaddition

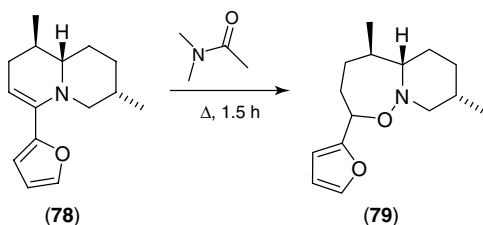
Inspired by the cycloaddition of the Palladium trimethylenemethane complexes reported by B. Trost, R. Shintani, and T. Hayashi [47] described the cycloaddition of nitrones with  $\gamma$ -methylene- $\delta$ -valerolactone **74**. The use of chiral ligands such as **77** furnished the oxazepine **76** in excellent yield, as well as dia- and enantioselectivity (Scheme 8.27).

### 8.2.1.4 Rearrangements

Some rearrangements, in natural product series, have been found to provide the 1,2-oxazepines in good preparative yields and deserve to be noticed herein [48]. Thus, (+)-nupharidine (**78**) (Scheme 8.28) furnished 1,2-oxazepine **79** in 65% yield



Scheme 8.27



Scheme 8.28

upon simple heating in dimethyl acetamide (DMA) for 1.5 h. A stereoselective reaction was observed but the configuration of the new formed chiral center was not determined [49].

### 8.2.2

#### 1,3-Oxazepines

The two heteroatoms in this type of compounds can form a *N,O*-acetal or a carbamate function. This would dictate the mode of formation of the heterocycle.

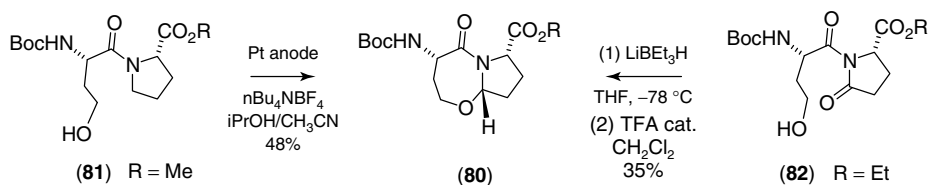
##### 8.2.2.1 *N,O*-Acetals

**Iminium Cyclization** The formation of a *N,O*-acetal was classically obtained through an iminium cyclization. The iminium ion can be classically formed by oxidative or reductive methods or by *in situ* condensation of a secondary amine with an aldehyde. This is illustrated herein in the preparation of similar peptidomimetic derivatives.

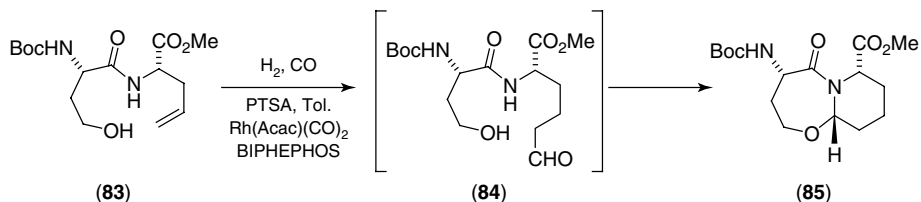
In the synthesis of peptidomimetic **80** described by Moeller [50], the iminium was formed by the anodic oxidation of the proline-homoserine dipeptide **81** and trapped *in situ* to give regio- and stereoselectively the pyrrolooxazepine (Scheme 8.29). The same product was obtained by Zhang [51] in 2001, but in this case the partial and selective reduction of the lactam function of a pyroglutamic-homoserine derivative **82** furnished the iminium.

A similar compound was recently prepared through the Rh catalyzed hydroformylation of the dipeptide **83** (Scheme 8.30). The so-formed intermediate aldehyde **84** allowed the formation of the *N,O*-acetal of the piperidinoxazepine **85** derivative with complete stereoselectivity [52].

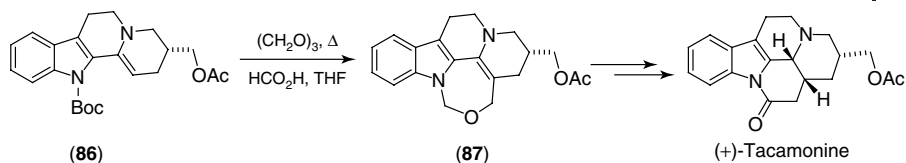
In the synthesis of alkaloid (+)-tacamonine, an interesting insertion of two formaldehyde units were reported to occur in high yield to give the pentacycle **87**,



Scheme 8.29



Scheme 8.30



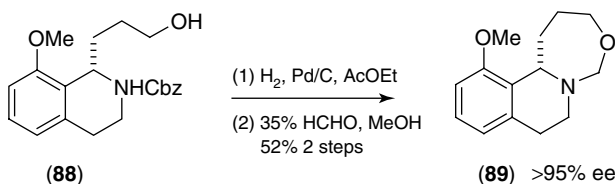
Scheme 8.31

which was stereoselectively reduced to the indoloquinolizidinooxazepine allowing the introduction of two of the stereogenic centers of natural tacamonine (Scheme 8.31) [53].

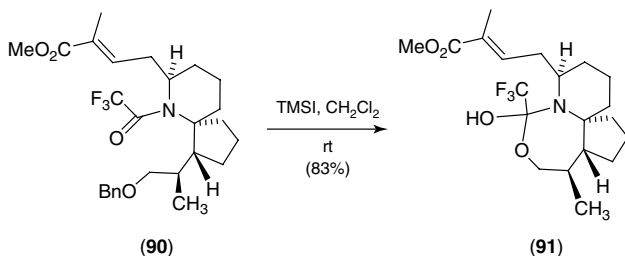
Formaldehyde was also used to attain the oxazepine skeleton in the synthesis of analogs of quinocarcin [54]. The treatment of the amino alcohol, resulting from the Cbz deprotection of **88**, with formol furnished the tricyclic compound **89** in 52% overall yield and >95% ee (Scheme 8.32).

An interesting while undesired cyclization to an oxazepine was observed in the course of the synthesis of pinnaic acid. This was obtained during the trimethylsilyl-iodide (TMSI) cleavage of the *O*-benzyl group of intermediate **90** to give **91** in 83% yield [55] (Scheme 8.33). This reaction may constitute an interesting access to oxazepine derivatives and, moreover, shows the high electrophilicity of the trifluoroacetyl group.

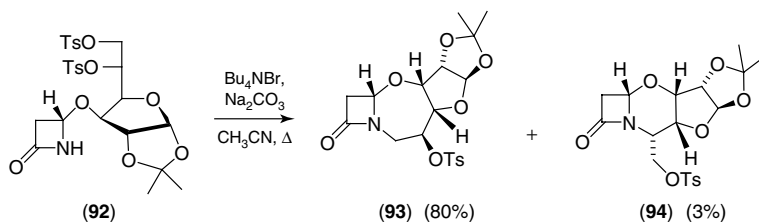
**Nucleophilic Displacement** The 1,3-oxazepine skeleton has been formed in very good yield by an intramolecular nitrogen alkylation of  $\beta$ -lactam **92** (Scheme 8.34) [56]. Only very minor amount (3%) of the expected six-membered ring **94** was found in this process while the seven-membered ring **93** was isolated in 80% yield.



Scheme 8.32



Scheme 8.33

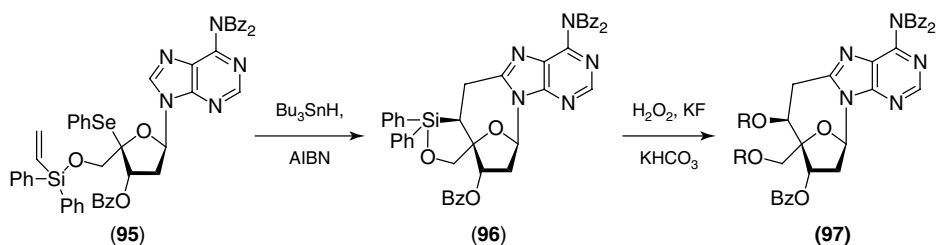


**Scheme 8.34**

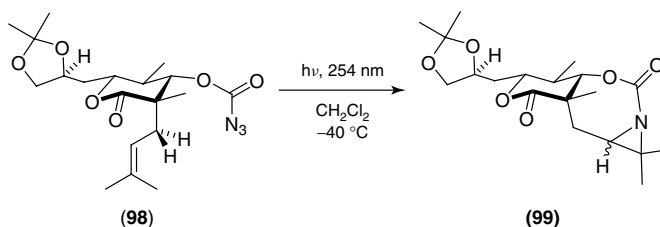
**Radical Cyclization** A tandem radical cyclization was observed when the phenyleneselenium derivative **95** was treated with Bu<sub>3</sub>SnH and AIBN in benzene. The second cyclization gave the seven-membered ring compound **96**, which upon Tamao conditions furnished the cyclonucleoside **97** in 35% overall yield (Scheme 8.35) [57].

**Carbamates** The nitrogen and the oxygen of the 1,3-oxazepine may be linked in a carbamate function. This function can be classically obtained from the corresponding amino alcohol. Indeed, in the examples found in the literature, the oxazepine was an undesired by-product obtained by the nucleophilic attack of an alcohol on the amide or carbamate protecting group [58]. Similarly, the photolysis of azido derivative **98** gave rise to the olefine aziridination in 85% yield, instead of the expected nitrene insertion at the allylic position (Scheme 8.36) [59].

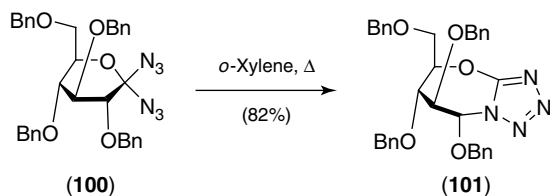
**Others** In sugar series, the thermal treatment of diazides such as **100** led to the formation of a tetrazole ring with enlargement of the sugar ring to a 1,3-oxazepine skeleton in a very good yield (Scheme 8.37) [60]. The reaction was also reported through photolysis giving 1,3- and 1,2-oxazepines [61].



**Scheme 8.35**



**Scheme 8.36**



Scheme 8.37

## 8.2.3

## 1,4-Oxazepines

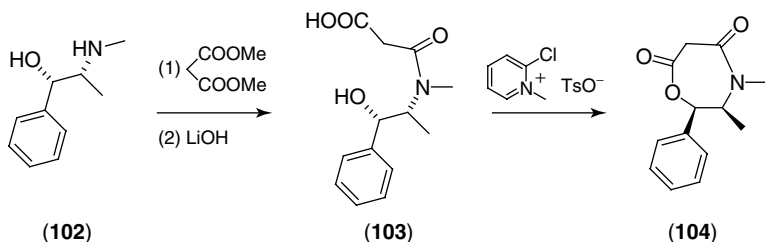
## 8.2.3.1 Amino Alcohol Double Condensation

Formally, the condensation of a  $\beta$ -amino-alcohol with a 1,3-bis-electrophilic derivative should lead to the 1,4-oxazepine skeleton. This strategy was classically used with different electrophilic functions. In the following example (Scheme 8.38), ephedrine (**102**) was condensed with dimethyl malonate to construct the oxazepine skeleton in a sequential three-step reaction. The first two steps were the amide formation and the saponification to the acid **103**. The latter was eventually lactonized through the use of 2-chloro-1-methylpyridinium tosylate to give the optically pure oxazepinedione **104** in 55% overall yield [62].

The double condensation of a  $\beta$ -amino alcohol with a  $\alpha$ -haloacetate was also reported. The reaction could be conducted in one step and necessitated the use of a base reagent such as NaH [63]. A more sophisticated and interesting synthesis was also reported by Bartlett [64] starting from alaninol. The condensation of the D-amino alcohol with aldehydo- $\alpha,\beta$ -unsaturated amide **105** was catalyzed by tin triflate and furnished the bicyclic pyrrolidino-oxazepine **106** in very good yield and diastereoselectivity (Scheme 8.39). In this synthesis, a thermodynamic control allowed the reaction to occur stereoselectively with formation two new chiral centers. Interestingly, condensation of the same compound with L-alaninol led to the enantiomer **109** of the target compound as the result of a difficult cyclization of **107**, which equilibrated to **108** after ring opening to the iminium intermediate.

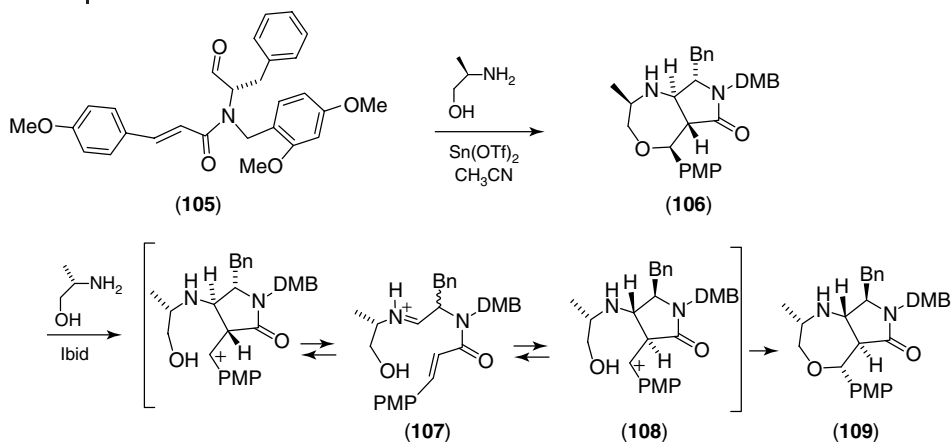
## 8.2.3.2 Other Cyclization Methods

Lactamization, lactonization, and transacetalization are classical reactions allowing cyclization to 1,4-oxazepines.



Scheme 8.38





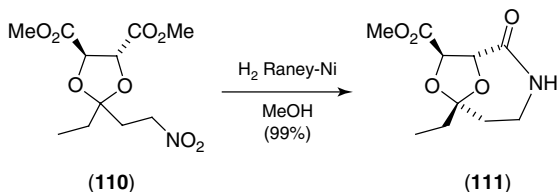
Scheme 8.39

Lactamization of chiral aminoesters was often used to attain the oxazepinone skeleton. The chirality was already installed on the framework of the amino esters [65]. In the following scheme (Scheme 8.40) [66], upon reduction of the nitro group of the chiral nitroketal **110** derived from dimethyl tartrate, spontaneous lactamization occurred to give almost quantitatively the optically active bicyclic oxazepinone **111**.

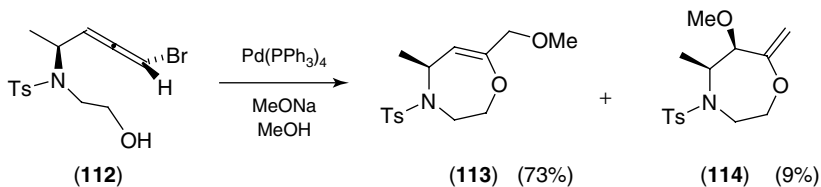
Similarly, the final cyclization may be the result of lactonization [67] or transacetalization [68, 69]. In all cases, the chirality was brought from chiral amino alcohol which was or not protected. Intramolecular opening of a chiral epoxide by an amino group was also reported to give the oxazepine in good yield [70].

### 8.2.3.3 Pd-Catalyzed Allene Cyclization

Tanaka *et al.* [71] have investigated the reaction of a bromoallene, which can act as a dication equivalent in the presence of Pd catalyst. When the bromoallene also bore an amino alcohol group, a cyclization could occur to give a ring containing a nitrogen and an oxygen. Following this methodology, the preparation of oxazepine was reported. Thus, (*S,aS*)-bromoallene **112**, in the presence of sodium methylate in methanol and of 5 mol% of  $\text{Pd}(\text{PPh}_3)_4$ , was transformed into oxazepine **113** in 73% yield, which represented the major regioisomer (9% of isomer **114** was also isolated) (Scheme 8.41).



Scheme 8.40



Scheme 8.41

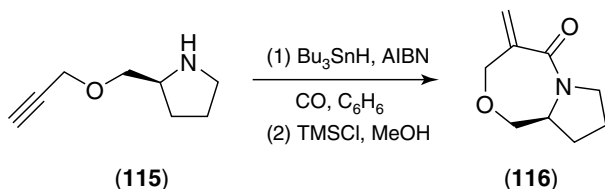
#### 8.2.3.4 Radical Cyclization

The intramolecular nucleophilic carbonyl trapping of an  $\alpha$ -ketenyl radical by an amino group allowed Ryu [72] to propose an original and efficient preparation method of nitrogen heterocycles. This method is general enough to be used for the access of oxazepines. Alkynylamine **115**, prepared from prolinol, was treated in benzene at  $90^\circ\text{C}$  for 3 h with tributyltin hydride under CO pressure of 75 atm using AIBN as initiator, to give the  $\alpha$ -methylene-oxazepinone **116** in 52% yield after protodestannylation ( $\text{TMSCl}$ ,  $\text{MeOH}$ ) (Scheme 8.42).

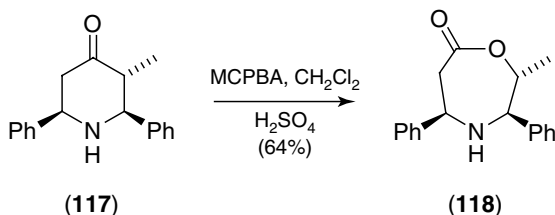
#### 8.2.3.5 Ring Enlargement

Several papers reported on the preparation of asymmetric 1,4-oxazepine via the ring enlargement of a six-membered ring. One way to this ring transformation was the Baeyer–Villiger oxidation of a piperidinone to the oxazepine. Thus, the *m*-chloroperbenzoic acid (MCPBA) oxidation of the piperidine-4-one **117**, in the presence of sulfuric acid (to protect the basic nitrogen), gave a 64% yield of oxazepine **118** as a unique regio- and stereomer [73] (Scheme 8.43).

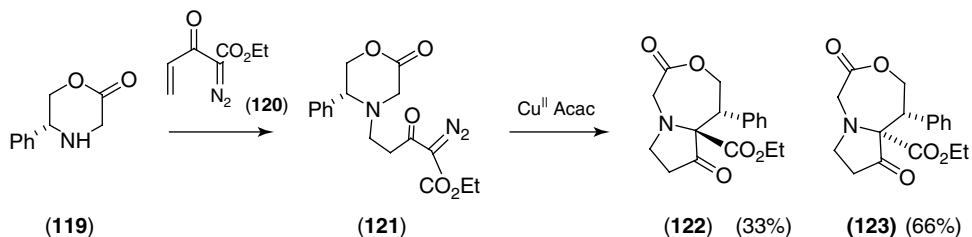
The [1,2]-Stevens rearrangement was also reported to perform a six- to seven-membered ring enlargement. In the following example (Scheme 8.44), the rearrangement of a cyclic ammonium ylide offered a simple and efficient route to chiral nonracemic cyclic amines. The key intermediate **121** was obtained in 80% yield by



Scheme 8.42



Scheme 8.43



Scheme 8.44

the conjugate addition of (*R*)-5-phenylmorpholin-2-one **119** to the diazo compound **120**. The copper(II) acetyl acetonate (ACAC) catalyzed reaction of the diazo intermediate **121** in boiling toluene provided quantitatively the easily separable bicyclic rearranged diastereomers **122** and **123** [74].

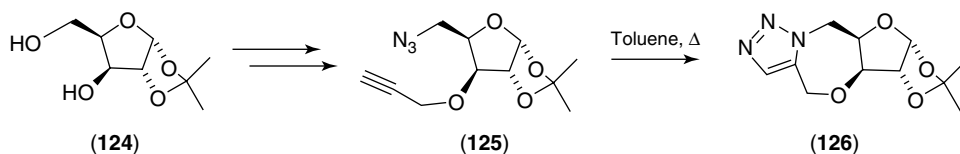
#### 8.2.3.6 Cycloaddition

The cycloaddition of azides with an unsaturated bond (Huisgen 1,3-dipolar cycloaddition) to give rise to triazole derivatives also offers an efficient method to access various heterocycles when it proceeds in an intramolecular fashion. In particular, performing the 1,3-dipolar cycloaddition reaction on carbohydrate-derived azido-alkynes (or alkene [75]) should offer good opportunity to the construction of bicyclic chiral triazolo-oxazepines. Starting from xylofuranosyl diol **124**, the primary alcohol function was transformed to the azido derivative via a classical sequence and the secondary alcohol function then converted to the propargyl ether **125** (Scheme 8.45). The cycloaddition was obtained by simple heating of **125** in toluene at 100 °C for 2 h resulting in the formation of **126** in 95% yield [76].

### 8.3

#### Thiazepines

Few works have been reported on the asymmetric preparation of chiral thiazepines probably because sulfur-containing starting materials are rare. Most of the thiazepines described so far are 1,4-thiazepines. Despite the similarity with oxazepines, most of the preparations are different.



Scheme 8.45

## 8.3.1

## 1,2-Thiazepines

The 1,2-thiazepines are only represented by cyclic sulfonamides and their preparation methods are classical ones, the chiral pool being used in order to introduce the chirality.

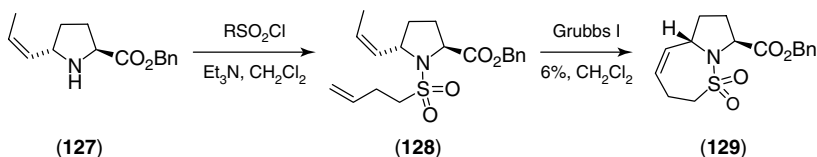
In the synthesis of bicyclic sulfonamide **129** reported by S. Hannessian [77] as a constrained proline analog, 2-propenyl derivative **127** was prepared from proline and treated with but-3-ene-1-sulfonyl chloride to give **128** in 55% yield. An ring closure metathesis (RCM) with first generation Grubbs catalyst furnished the bicyclic sulfonamide **129** in 81% yield.

A cyclic sulfonamide was described in the synthesis of enantiopure 4-phenyl pyrrolidine-2-yl-methanol. In this synthesis (Scheme 8.47), the sulfonamide **130** obtained in two steps from hydroxyproline was transformed to the 2,5-dihydropyrrole **131**, which was subjected to a Heck reaction furnishing a 1 : 1 mixture of benzosulfonamides **132**. Interestingly, protection of the primary alcohol as a bulky pivaloyl ester gave a stereoselective Heck reaction.

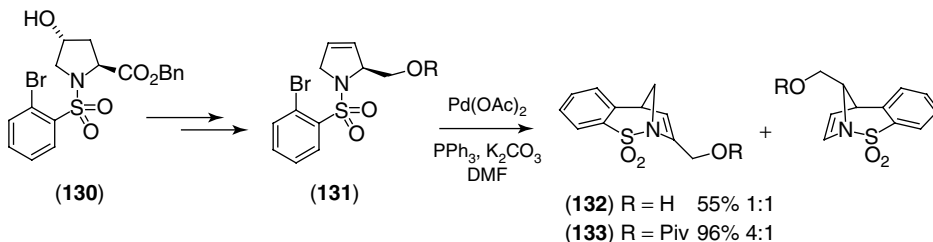
## 8.3.2

## 1,3-Thiazepines

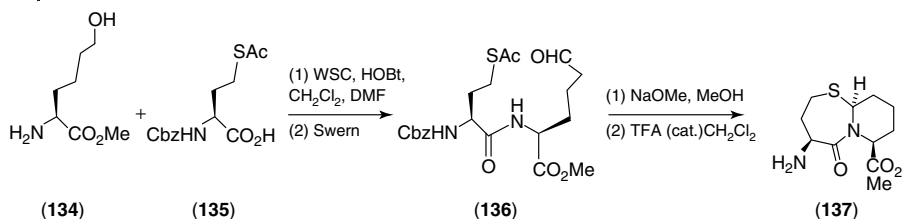
Bicyclic thiazepinone was prepared as dipeptide mimetics with metalloprotease inhibitor properties [78]. The synthesis, in this case, parallels the synthesis of oxazepine via the cyclization into iminium ions (cf Section on Iminium Cyclization). Homocysteine derivative **135** was resolved from racemic material and condensed with hydroxynorleucine **134** (enzymatically resolved) and the dipeptide was oxidized to aldehyde **136** (Scheme 8.48). The deprotection of the thiol was followed by the acid promoted cyclization and Cbz removal to **137**.



Scheme 8.46



Scheme 8.47



Scheme 8.48

## 8.3.3

## 1,4-Thiazepines

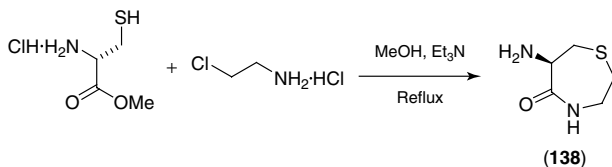
The 1,4-thiazepines are the most frequently described thiazepines. Several asymmetric syntheses are available. In most of the cases, the chirality was introduced as a fragment arising from the chiral pool; cysteine and penicillamine are the most common. Curiously, the syntheses are specific ones and very few follow the strategy encountered with 1,4-diazepine or oxazepine counterparts.

## 8.3.3.1 From Mercaptopropionic Acid Derivatives

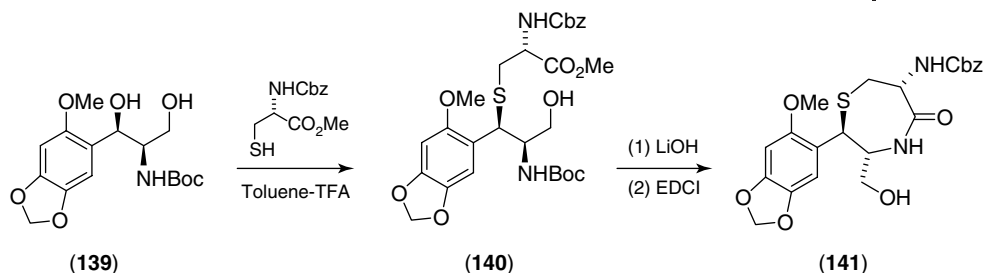
We will find in this category the achiral mercapto acids as well as cysteine or penicillamine. The two last compounds react at the thiol and acidic functions of the mercapto acids; thus the acids react with a 3-atom fragment possessing a nitrogen and an electrophilic function.

**Condensation with Haloethylamine, β-Amino Alcohol, and Derivatives** The condensation of cysteine with haloethylamine has been used recently in a one-pot process to prepare thiazepine with ICE (interleukin converting enzyme) inhibitor properties. A simple reflux in methanol, in the presence of NEt<sub>3</sub>, of L-cysteine methyl ester hydrochloride and 2-chloroethylamine hydrochloride allowed the condensation to occur furnishing 1,4-thiazepine **138** [79] (Scheme 8.49). This reaction illustrates a type of condensation that was used with various reagents and generally in a multistep process.

The condensation of cysteine with a chiral β-haloamine, for example, allowed the introduction of new chiral centers on the seven-membered ring. The first step of the sequence was the sulfur alkylation, which was followed by a peptide coupling [80]. Reaction of cysteine with a chiral amino alcohol was also reported; in this case the final cyclization was obtained after activation of the OH function as a mesylate [81]. Zhu [82] recently reported on the *N*-carbamate-assisted stereoselective substitution



Scheme 8.49

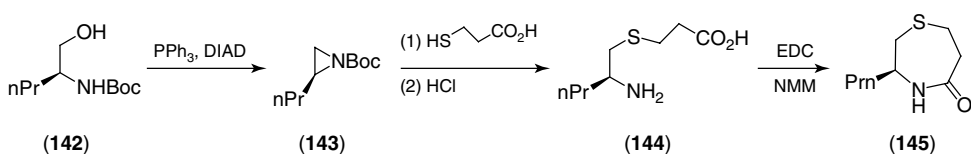


Scheme 8.50

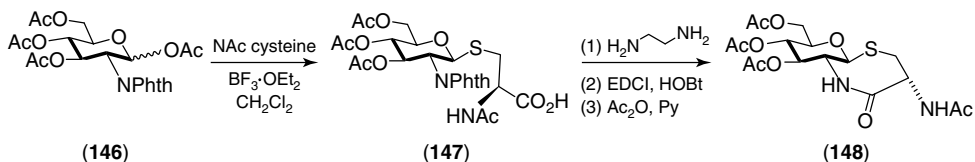
of benzylic hydroxyl group by thiol. Simple treatment of a benzylic alcohol having a neighboring carbamate function with a thiol in the presence of TFA led to the introduction of the thiol with retention of configuration. This was applied to compound **139** and cysteine, which gave **140** with complete stereocontrol and the latter was cyclized with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to furnish the thiazepine **141**.

Reactions with achiral mercaptopropionic acid were also reported; chiral aziridine [83] or amino acid [84] was used as the 3-atom fragment. In the preparation of thiazepanes as inhibitors of nitric oxide synthase, the amino alcohol **142** was the precursor of the aziridine **143** via a Mitsunobu reaction (Scheme 8.51). Addition of  $\beta$ -mercaptopropionic acid furnished the amino acid **144**, which was cyclized to **145** via conventional methods.

**Condensation with Nitro Olefine** The research of new active inhibitors of ACE led Japanese researchers to propose an interesting access to thiazepine through the Michael addition of cysteine onto a nitro olefine [85]. In this sequence a new chiral center was formed. Unfortunately, there is no report of the diastereoselectivity of the Michael addition. The reduction of the nitro group into a primary amine allowed the final cyclization through lactamization. The final product was obtained in enantiomerically pure form after recrystallization.



Scheme 8.51



Scheme 8.52

**Condensation with Amino Sugar** Fused bicyclic glycosides–thiazepines have been prepared by the reaction of the phthalimido-protected sugar **146**, used as donor, with N-acetylated L-cysteine [86] (Scheme 8.52). This ensured the introduction of cysteine at the anomeric center as the desired  $\beta$ -thioglycoside. Selective removal of the N-phthalimido group was obtained by treatment with ethylenediamine in methanol and the free amino group was reacted with EDCI/hydroxybenzotriazole (HOBt) to give the bicyclic product in 50% yield.

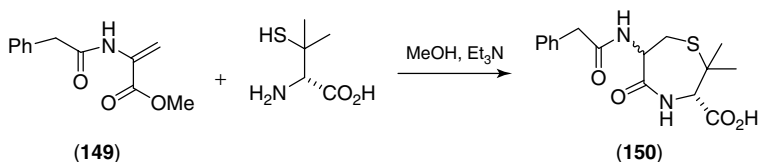
**Cysteine in  $S_NAr$  Reaction** Benzothiazepine compounds have been prepared in the search of new effective inhibitors of ACE. One of these syntheses paralleled the synthesis of benzodiazepine (cf Section on Via an  $S_NAr$  Reaction) starting with a  $S_NAr$  reaction of N-Ac cysteine on 2-fluoronitrobenzene. The reduction of the nitro group into primary amine was followed by lactamization to give the required benzothiazepine [87].

### 8.3.3.2 From Amino Thiols

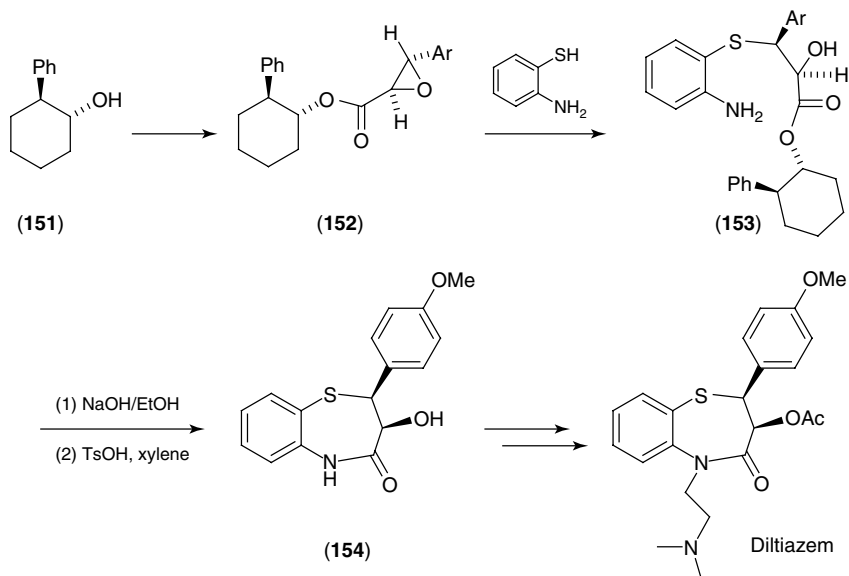
Aminothiols were also broadly used as sulfur reagents in the preparation of thiazepines. Since the aminothiols are bis-nucleophile derivatives, the counterpart in this condensation should possess two electrophilic functions.

**Aminothiols and Acrylic Acid Derivatives** The most frequently used reactants were acrylic acid and its analogs [88]. Thus, as illustrated in Scheme 8.53, D-penicillamine was reacted with  $\alpha$ -phenylacetamidoacrylate (**149**) in the presence of  $Et_3N$  to give the expected thiazepine **150**, unfortunately as a mixture of stereoisomers without indication of the ratio [89].

**Aminothiols and Other Dielectrophilic Compounds** Diltiazem, a calcium channel blocker, is probably the most representative compound of thiazepines. Several syntheses were published but very few were asymmetric ones. Researchers from Hoffmann-La Roche published an efficient synthesis [90] in which the condensation of 2-aminobenzenethiol to an enantiomerically pure epoxy ester **152** allowed the preparation of diltiazem in asymmetric form (Scheme 8.54). The synthesis was based on the lipase-catalyzed kinetic resolution of *trans*-2-phenylcyclohexanol to give the pure (–)-1*R*,2*S* enantiomer **151**. This compound was the chiral source to attain pure glycidic ester **152** via a Darzens reaction. 2-Aminobenzenethiol reacted with **152** in refluxing toluene to give **153** with the expected configuration. Deprotection of **153** was followed by acidic treatment, which allowed cyclization to occur.



Scheme 8.53

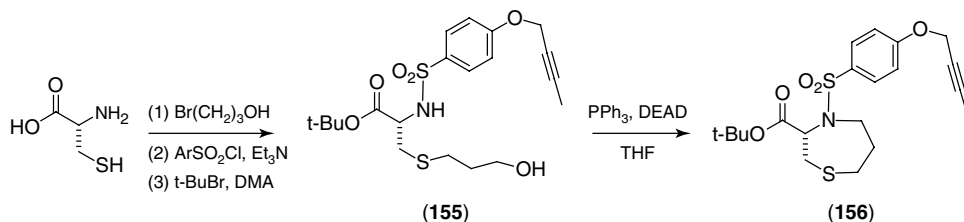


Scheme 8.54

Dihalopropan and halopropanol were also used in the condensation of aminothiols. A one-step reaction was claimed to occur by condensation of 3-chlorobromopropane with penicillamine [91]. In the following example (Scheme 8.55) [92], the first step was the sulfur alkylation of cysteine with bromopropanol, which was followed by N-sulfonylation to give **155**. The final cyclization was achieved by a Mitsunobu reaction to give the thiazepine **156** as depicted in Scheme 8.55.

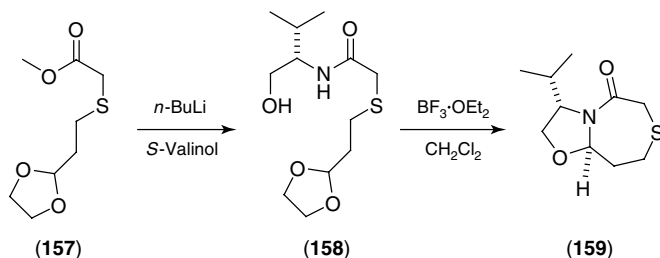
### 8.3.3.3 Others

Recently, Gleason [93] reported a study devoted to the asymmetric construction of quaternary centers on the basis of the use of the 5,7-bicyclic thioglycolate **159**. An interesting, short and straightforward preparation of **159** was proposed, which was like the Meyer's lactam synthesis. In the present preparation, achiral methyl thioglycolate was alkylated with 2-bromoethyl dioxolane and the obtained ester **157** used to N-acylate *S*-valinol (Scheme 8.56). The resulting amide **158** underwent a



Scheme 8.55





Scheme 8.56

transacetalization to give the expected bicyclic compound **159**, in an excellent 71% overall yield and as a single stereoisomer.

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